C H A P T E R 18

DRUGS AND THE TREATMENT OF PSYCHIATRIC DISORDERS

Psychosis and Anxiety

Ross J. Baldessarini

Since the 1950s, drugs with demonstrated efficacy in a broad range of severe psychiatric disorders have been developed, leading to the emergence of the subspecialty of psychopharmacology. Knowledge of the actions of such agents has greatly stimulated research in biological psychiatry aimed at defining pathophysiological changes. This chapter reviews current knowledge of the pharmacology of antipsychotic and antianxiety agents; antimanic, mood-stabilizing, and antidepressant agents are covered in Chapter 19.

*Effective antipsychotic (neuroleptic) agents include tricyclic phenothiazines, thioxanthenes, and dibenzepines, as well as butyrophenones and congeners, other heterocyclics, and experimental benzamides. Virtually all block D2 dopaminergic receptors and inactivate dopamine neurotransmission in forebrain; some also interact with D1 dopaminergic, 5-HT$_2$ serotonergic, and α-adrenergic receptors. The recent discovery of additional dopamine receptor subtypes may lead to further innovations. Neuroleptics are highly lipophilic, metabolized mainly by hepatic oxidative mechanisms, and may have complex elimination kinetics. These drugs have been shown to offer effective palliative treatment of organic or idiopathic psychotic disorders with acceptable safety and practicality. Agents of high potency have more acute extrapyramidal neurological effects, and low-potency agents induce more sedative, hypotensive, and autonomic side effects. Treatment of acute psychotic illness typically involves daily doses up to the equivalent of 10 to 20 mg of fluphenazine or haloperidol (at serum concentrations of about 5 to 20 ng/ml) or 300 to 600 mg of chlorpromazine; higher doses are not usually more effective, long-term maintenance treatment usually requires lower doses, and tolerance virtually is unknown. Most neuroleptics induce characteristic neurological side effects (dystonia, akathisia, bradykinesia, dyskinesias); several atypical agents (*e.g.*, clozapine and risperidone in low doses) have limited extrapyramidal side effects.*

The pharmacological treatment of anxiety disorders currently is based primarily on the use of benzodiazepine sedative-antianxiety agents, which facilitate neuronal hyperpolarization through the gamma-aminobutyric acid-receptor–Cl$^-$ channel macromolecular complex. Unlike many psychotropic agents, the clinical actions of benzodiazepines are best understood as a reflection of their early absorption rates and distribution kinetics. Potent benzodiazepines are effective in panic disorder as well as in generalized anxiety disorder. Their long-term risk:benefit ratio remains controversial. Serotonin 5-HT$_{1A}$ partial agonists such as buspirone also have useful anxiolytic and other psychotropic activity, and less likelihood of inducing sedation or dependence. Specialized uses of antidepressants discussed in the following chapter include the treatment of certain severe anxiety disorders.

INTRODUCTION: HISTORY AND NOSOLOGY

The use of drugs with demonstrated efficacy in psychiatric disorders has become widespread since the mid-1950s. Today, about 10% to 15% of prescriptions written in the United States are for medications intended to affect mental processes: to sedate, stimulate, or otherwise change mood, thinking, or behavior. This practice reflects both the high frequency of primary psychiatric disorders and the nearly inevitable emotional reactions of persons with medical illnesses. In addition, many drugs used for other purposes also modify emotions and cognition either as part of their usual actions or as toxic effects of overdosage (*see* especially Chapter 24). This and the following chapter discuss psychotropic agents used primarily for the treatment of psychiatric disorders. The study of the chemistry, disposition, actions, and clinical pharmacology of such drugs has led to development of the specialty widely known as *psychopharmacology*.

Psychotropic agents can be placed into four major categories. *Antipsychotic* or *neuroleptic* drugs are those used to treat very severe psychiatric illnesses, the psychoses and mania; they have beneficial effects on mood and thought but carry the risk of producing characteristic side effects that mimic neurological diseases. *Antianxiety-sedative* agents, particularly the benzodiazepines, are those used for the drug therapy of anxiety disorders. *Antidepressants* (mood-elevating agents) and antimanic or *mood-stabilizing* drugs (notably, lithium salts and certain anticonvulsants) are those used to treat affective or mood disorders and related conditions (*see* Chapter 19).

The use of drugs in the treatment of psychiatric disorders is becoming more precise as psychiatric diagnoses continue to gain objectivity, coherence, and reliability. Searches for biological bases of psychiatric illnesses have been stimulated by knowledge of the mechanisms of action of psychotropic agents and the emergence of a medical discipline commonly known as *biological psychiatry* (Weil-Malherbe, 1967; Baldessarini, 1996a). The diagnostic terminology and criteria for psychiatric disorders currently employed in the United States are well described in the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (1994).

History. Modification of behavior, mood, and emotion by drugs always has been a favorite practice of human beings. The use of psychoactive drugs evolved along two related paths: the use of drugs to modify normal behavior and to produce altered states of feeling for religious, ceremonial, or recreational purposes and their use to alleviate mental ailments. Fascinating accounts of the early history and characteristics of many psychoactive compounds, particularly those derived from natural products, are presented by Lewin (1931) and Efron and associates (1967). In 1845, Moreau proposed that hashish intoxication provided a model psychosis useful in the study of insanity. Three decades later, Freud presented his study of cocaine and suggested its potential uses in pharmacotherapy. Soon thereafter, Kraepelin founded the first laboratory of clinical psychopharmacology in Germany and evaluated psychological effects of drugs in humans. In 1931, Sen and Bose published the first report of the use of *Rauwolfia serpentina* in the treatment of insanity (*see* Shore and Giachetti, 1978). Insulin shock, pentylenetetrazol-induced convulsions, and electroconvulsive therapy followed in 1933, 1934, and 1937, respectively. Treatments for both major depression and schizophrenia thus became available. Amphetamine (a congener of ephedrine, an active component of the Chinese herbal agent *ma huang*) was the first synthetic drug to provide a model psychosis. In 1943, Hofmann ingested a minute amount of the ergot derivative lysergic acid diethylamide (LSD) and experienced its hallucinogenic effects. His report of the high potency of LSD popularized the concept that a toxic substance or product of metabolism might be a cause of mental illness.

The first modern report on the treatment of psychotic excitement or mania with lithium salts was that of Cade (1949). Because of concerns about the toxicity of lithium, this discovery was slow in gaining general acceptance by the medical community. In 1950, chlorpromazine was synthesized in France. The recognition of the unique effects of chlorpromazine by Laborit and colleagues (1952) and its use in psychiatric patients by Delay and Deniker (1952) marked the beginnings of modern psychopharmacology. The history of this revolutionary era in psychiatric therapeutics is recounted by Ayd and Blackwell (1970). The term *tranquilizer* was introduced in the early 1950s by Yonkman to characterize the psychic effect of reserpine. Despite its popularity, this term is ambiguous and misleading.

A report on meprobamate by Berger (1954) marked the beginning of investigations of modern sedatives with useful antianxiety properties. An antitubercular drug, iproniazid, was introduced in the early 1950s and soon was recognized as a monoamine oxidase inhibitor and antidepressant (Kline, 1958); in 1958, Kuhn recognized the antidepressant effect of imipramine. The first of the antianxiety benzodiazepines, chlordiazepoxide, was developed by Sternbach in 1957. In the following year Janssen discovered the antipsychotic properties of haloperidol, a butyrophenone (*see* Janssen, 1974), and thus still another class of antipsychotic agents became available. During the 1960s the expansion of psychopharmacological research was rapid, and many new theories of psychoactive drug effects were introduced. The clinical efficacy of many of these agents was firmly established during that decade.

For many years, the role of biogenic amines and their receptors in the CNS in mediating effects of psychotropic drugs has been emphasized and has stimulated searches for the causes of mental illness. In addition, increasing attention has been paid to the liabilities of treatment with psychotherapeutic drugs, especially their limited efficacy in severe or chronic mental illnesses, their risk of sometimes serious toxic effects, and the limitations of screening and testing methods used to develop new agents. The antipsychotic, mood-stabilizing, and antidepressant agents used to treat the most severe mental illnesses have had a remarkable impact on psychiatric practice and theory—an impact that legitimately can be called revolutionary and one that is experiencing continued innovation.

Nosology. The different classes of psychotropic agents are selective in their ability to modify symptoms of mental illnesses. The optimal use of such drugs thus requires familiarity with the differential diagnosis of psychiatric conditions (*see* Kaplan and Sadock, 1989; American Psychiatric Association, 1994). A few salient aspects of psychiatric nosology (the science of the classification of diseases) are summarized briefly here, and additional information is provided in the discussion of specific classes of drugs.

Basic distinctions are made among the psychoses, cognitive disorders, mood disorders, anxiety disorders, and disorders of personality. The psychoses are among the most severe psychiatric disorders, in which there is not only marked impairment of behavior but also a serious inability to think coherently, to comprehend reality, or to gain insight into the presence of these abnormalities. The psychoses commonly include symptoms of false beliefs (*delusions*) and abnormal sensations (*hallucinations*). The psychotic disorders are suspected of having a neurobiological basis, but usually are distinguished from the cognitive disorder syndromes of *delirium* and *dementia*.

The cognitive disorders commonly are associated with definable neuropathological, metabolic, or toxic (including drug-induced) changes and are characterized by confusion, disorientation, and memory disturbances as well as behavioral disorganization. In general, the effectiveness of pharmacological treatment of the core cognitive impairment in the dementias remains limited, despite extensive efforts to develop effective treatments. These have included use of stimulants, so-called noötropics (*e.g.*, periacetam), cholinesterase inhibitors (Knapp *et al.*, 1994), putative cerebral vasodilators (*e.g.*, ergot alkaloids, papaverine, isoxuprine), and the calcium channel blockers such as nimodipine (*see* Chapters 33 and 34). This topic is not specifically covered in this chapter, but is discussed elsewhere (*see* Baldessarini, 1996b).

The etiological basis of other psychotic disorders remains unknown, although genetic and neurodevelopmental as well as environmental causative factors have been proposed. Representative syndromes in this category include schizophrenia, brief psychoses, and delusional disorders, although psychotic features also are not uncommon in the major mood disorders, particularly mania and severe depression. The psychotic illnesses are characterized by disorders of thinking processes as inferred from illogical or highly idiosyncratic communications, with disorganized or irrational behavior and varying degrees of altered mood that can range from excited agitation to severe emotional withdrawal. Idiopathic psychoses characterized mainly by chronically disordered thinking and emotional withdrawal and often associated with delusions and auditory hallucinations are called *schizophrenia*. Acute or recurrent idiopathic psychoses also occur that bear an uncertain relationship to schizophrenia or the major affective disorders. In addition, more or less isolated delusions can arise in *delusional disorder* or *paranoia*.

The major disorders of mood or affect include the syndromes of major depression (formerly including melancholia) and bipolar disorder (formerly manic-depressive disorder). They commonly include disordered autonomic functioning (*e.g.*, altered activity rhythms, sleep, and appetite) and behavior, as well as persistent abnormalities of mood and increased risk of self-harm or suicide. These disorders are discussed in Chapter 19.

Antipsychotic drugs exert beneficial effects in many types of psychotic illness and are *not* selective for schizophrenia. Their beneficial actions are found in disorders ranging from postsurgical delirium and amphetamine intoxication to paranoia, mania, and psychotic depression, and they can be beneficial against the agitation of Alzheimer's dementia. They are especially beneficial in severe depression and possibly other conditions marked by severe anxiety or agitation. Thus, in general, psychotropic drugs are not disease-specific: they provide clinical benefit for a range of syndromes. However, as noted later in this chapter, they are not appropriate for routine use in most anxiety disorders.

The less pervasive psychiatric disorders include the neuroses or anxiety-associated disorders. Whereas the ability to comprehend reality is retained, suffering and disability are sometimes very severe. Neuroses may be acute and transient or, more commonly, persistent or recurrent. Their symptoms may include mood changes (anxiety, panic, dysphoria) or limited abnormalities of thought (obsessions, irrational fears) or of behavior (rituals or compulsions, pseudoneurological or "hysterical" conversion signs). In such disorders, drugs may have some beneficial effects, particularly by modifying associated anxiety and depression and so facilitating a more comprehensive program of treatment and rehabilitation. Because of the side effects of most of the available antipsychotic agents, their use should be reserved for appropriately severe illnesses. They have only a limited role in the treatment of affective disorders, which often require prolonged treatment.

Other lifelong conditions, including the so-called personality disorders, may or may not respond to medical intervention. Many of these conditions include characteristic personality styles (*e.g.*, avoidant, paranoid, withdrawn, dependent, unstable). Other disorders involve patterns of behavior (*e.g.*, abuse of alcohol or other substances, deviant eating patterns, hypochondriasis, antisocial or other abnormal behaviors). Typically, drugs are not effective in such chronic conditions except when anxiety or depression occur; they also may be effective in some cases of bulimia or obsessive-compulsive disorder or in the medical management of withdrawal from addicting substances (*see* Chapter 24).

Biological Hypotheses in Mental Illness. The introduction in the 1950s of relatively effective and selective drugs for the management of schizophrenia and manic-depressive patients encouraged formulation of biological concepts of the pathogenesis of these major mental illnesses. In addition, other agents were discovered that mimic some of the symptoms of severe mental illnesses. These include LSD, which induces hallucinations and altered emotional states, and antihypertensive agents such as reserpine, which can induce depression. A leading hypothesis that arose from such considerations was based on observations indicating that antidepressants enhance the biological activity of monoamine neurotransmitters in the central nervous system (CNS) and that antiadrenergic compounds may induce depression. These observations led to speculation that a deficiency of aminergic transmission in the CNS might be causative of depression or that an excess could result in mania. Further, since antipsychotic agents antagonize the actions of dopamine as a neurotransmitter in the forebrain, it was proposed that there may be a state of functional overactivity of dopamine in the limbic system or cerebral cortex in schizophrenia or mania. Alternatively, an endogenous psychotomimetic compound might be produced either uniquely or in excessive quantities in psychotic patients.

This "pharmacocentric" approach to the construction of hypotheses is appealing and has gained support from studies of the actions of antipsychotic and antidepressant drugs, while also encouraging further development of similar agents. In turn, the plausibility of such biological hypotheses has encouraged interest in genetic studies, as well as in clinical biochemical studies. Despite extensive efforts, attempts to document metabolic changes in human subjects predicted by these hypotheses have not, on balance, provided consistent or compelling corroboration (Baldessarini, 1996a; Meltzer and Lowy, 1987; Weil-Malherbe, 1967). Moreover, results of genetic studies have provided evidence that inheritance can account for only a portion of the causation of mental illnesses, leaving room for environmental and psychological hypotheses.

The antipsychotic, antianxiety, antimanic, and antidepressant drugs have effects on cortical, limbic, hypothalamic, and brainstem mechanisms that are of fundamental importance in the regulation of arousal, consciousness, affect, and autonomic functions. It is quite possible that physiological and pharmacological modification of these brain regions has important behavioral consequences and useful clinical effects regardless of the fundamental nature or cause of the mental disorder in question. The lack of specificity of most psychotropic drugs for particular diseases tends to reduce the chances of finding a discrete metabolic correlate for a specific disease based simply on the actions of therapeutic agents. Finally, the technical problems associated with attempts to study changes in the metabolism or the postmortem chemistry of the human brain are formidable. Among these are artifacts introduced by drug treatment itself.

In summary, the available information does not permit a conclusion as to whether discrete biological lesions are the crucial basis of the most severe mental illnesses (other than the deliria and dementias). Moreover, it is not necessary to presume that such a basis is operative to provide effective medical treatment for psychiatric patients. Furthermore, it would be clinical folly to underestimate the importance of psychological and social factors in the manifestations of mental illnesses or to overlook psychological aspects of the conduct of biological therapies (Baldessarini, 1994, 1996b; Janicak *et al.*, 1993).

Identification and Evaluation of Psychotropic Drugs. Although rational development and assessment of the efficacy of any drug is problematic, the difficulties in evaluating psychoactive drugs are particularly challenging. The essential characteristics of human mental disorders cannot be reproduced in animals. Cognition, communication, and social relationships in animals are difficult to compare with human conditions. Thus, screening procedures in animals are of limited utility for the discovery of unique therapeutic agents. Contemporary pharmacology has provided many techniques for characterizing the actions of known psychotropic and other CNS agents at the cellular and molecular levels. Characteristics such as affinity for specific receptors or transporters can lead to the identification of new agents. Further innovation is anticipated from the rapid recent progress in identifying novel subtypes of classical neurotransmitter receptors and many other macromolecular target sites in brain tissue for potential new drugs (Baldessarini, 1996a, 1996b). In addition, clinical evaluation of new drugs is hampered by inhomogeneity of diagnostic groups and difficulty in application of valid, sensitive measurements of the effects of therapy. As a consequence, the results of clinical trials of psychotropic agents sometimes seem equivocal or inconsistent. Reviews of the principles and problems in identifying the efficacy and safety of psychotropic drugs are available (Baldessarini, 1996b; Janicak *et al.*, 1993).

I. Drugs Used in the Treatment of Psychoses

Several classes of drugs are effective in the symptomatic treatment of psychiatric disorders. They are most appropriately used in the therapy of schizophrenia, the manic phase of manic-depressive illness, and other acute idiopathic psychotic illnesses. They are also used as an alternative to electroconvulsive therapy (ECT) in severe depression with psychotic features and sometimes in the management of patients with organic psychotic disorders. Effective antipsychotic compounds include the *phenothiazines,* structurally similar *thioxanthenes,* and heterocyclic *dibenzazepines;* the *butyrophenones* (phenylbutylpiperidines) and *diphenylbutylpiperidines;* and the *indolones* and other heterocyclic compounds. The less effective *Rauwolfia alkaloids* and related amine-depleting agents are now only of historical interest. Since these chemically dissimilar drugs share many properties, information about their pharmacology and clinical uses is presented for the group as a whole. Particular attention is paid to chlorpromazine, the oldest representative of the phenothiazine–thioxanthene group of antipsychotic agents, and haloperidol, the original butyrophenone and representative of several related classes of aromatic butylpiperidine derivatives.

Many patients have been treated with the antipsychotic (neuroleptic) agents since their introduction in the 1950s. Although the antipsychotic drugs have had a revolutionary, beneficial impact on medical and psychiatric practice, their liabilities, especially their almost relentless association with extrapyramidal neurological effects, also must be emphasized (*see* Baldessarini, 1996b).

Antipsychotic agents are used primarily in the management of patients with psychotic or other serious psychiatric illnesses marked by agitation and impaired reasoning. These drugs have other properties that possibly are useful clinically, including antiemetic and antihistaminic effects

and the abil
eral anesthe
where in th
than three c
conditions
for other us
tations, at l
nent experi
receptor a
side effec
has been
associate
pine (disc
clinical us

History. Th
summarized
1950s, some
Rauwolfia pl.
was later che
and related c
from their ve
fects, these a
vere side eff
and depresse
has been as
Phenoth
nineteenth ce
methylene bl
thazine, was
to treat agita
antihistamin
Meanw
sleeping tim
into clinical
agent (Labo
phenothiazin
1949–1950
Laborit and
tentiate anes
mazine by it
arousal and
These centra
thereafter.
The fir
were made i
In 1952, De
achieved mo
that it had a
verse sympt
treal, follow
of chlorpron
tor exciteme
studies soon
ment of psy

Chemistry
viewed in d
a three-ring

and the ability to potentiate analgesics, sedatives, and general anesthetics; many of these actions are discussed elsewhere in this text (*see* Index). At the present time, more than three dozen neuroleptic drugs are used in psychiatric conditions worldwide; still others are marketed primarily for other uses. The term *neuroleptic* has taken on connotations, at least in the United States, of relatively prominent experimental and clinical antagonism of D2 dopamine receptor activity, with substantial risk of extrapyramidal side effects. In recent years, the term *atypical neuroleptic* has been used to describe antipsychotic agents that are not associated with extrapyramidal side effects of which *clozapine* (discussed later) is the principal example available for clinical use in the United States.

History. The history of the antipsychotic agents is especially well summarized by Swazey (1974) and Caldwell (1978). In the early 1950s, some antipsychotic effects were obtained with extracts of the *Rauwolfia* plant and then with large doses of pure reserpine, which was later chemically synthesized by Woodward. Although reserpine and related compounds that share its ability to deplete monoamines from their vesicular storage sites in neurons exert antipsychotic effects, these are relatively weak and are typically associated with severe side effects, including sedation, hypotension, diarrhea, anergy, and depressed mood. Thus, the clinical utility of reserpine primarily has been as an antihypertensive agent (*see* Chapter 33).

Phenothiazine compounds were synthesized in Europe in the late nineteenth century as part of the development of aniline dyes such as methylene blue. In the late 1930s a phenothiazine derivative, *promethazine*, was found to have antihistaminic and sedative effects. Attempts to treat agitation in psychiatric patients with promethazine and other antihistamines followed in the 1940s, but with little success.

Meanwhile, the ability of promethazine to prolong barbiturate sleeping time in rodents was discovered, and the drug was introduced into clinical anesthesia as a potentiating and autonomic stabilizing agent (Laborit *et al.*, 1952). This work prompted a search for other phenothiazine derivatives with anesthesia-potentiating actions, and in 1949–1950 Charpentier synthesized *chlorpromazine*. Soon thereafter, Laborit and colleagues described the ability of this compound to potentiate anesthetics and produce "artificial hibernation." Chlorpromazine by itself did not cause a loss of consciousness but diminished arousal and motility, with some increased tendency to promote sleep. These central actions became known as *ataractic* or *neuroleptic* soon thereafter.

The first attempts to treat mental illness with chlorpromazine were made in Paris in 1951 and early 1952 by Paraire and Sigwald. In 1952, Delay and Deniker became convinced that chlorpromazine achieved more than symptomatic relief of agitation or anxiety and that it had an ameliorative effect upon psychotic processes with diverse symptomatology. In 1954, Lehmann and Hanrahan in Montreal, followed by Winkelman in Philadelphia, reported the initial use of chlorpromazine in North America for the treatment of psychomotor excitement and manic states as well as schizophrenia. Clinical studies soon revealed that chlorpromazine was effective in the treatment of psychotic disorders of various types.

Chemistry and Structure–Activity Relationship. This topic is reviewed in detail elsewhere (Baldessarini, 1996a). Phenothiazine has a three-ring structure in which two benzene rings are linked by a sulfur and a nitrogen atom (*see* Table 18–1). If the nitrogen at position 10 is replaced by a carbon atom with a double bond to the side chain, the compound is a thioxanthene.

Substitution of an electron-withdrawing group at position 2 increases the efficacy of phenothiazines and other tricyclic congeners (*e.g.*, chlorpromazine *vs.* promazine). The nature of the substituent at position 10 also influences pharmacological activity. As can be seen in Table 18–1, the phenothiazines and thioxanthenes can be divided into three groups on the basis of substitution at this site. Those with an *aliphatic* side chain include *chlorpromazine* and *triflupromazine* among the phenothiazines; these compounds are relatively low in potency (but not in clinical efficacy). Those with a *piperidine* ring in the side chain include *thioridazine* and *mesoridazine*. There appears to be a lower incidence of extrapyramidal side effects with this substitution, possibly due to increased central antimuscarinic activity. Several potent phenothiazine antipsychotic compounds have a *piperazine* (or piperazinyl) group in the side chain: *fluphenazine* and *trifluoperazine* are examples. Use of these potent compounds, most of which have relatively weak anticholinergic activity, entails a greater risk of inducing extrapyramidal side effects but less tendency to produce sedation or autonomic side effects such as hypotension, unless unusually large doses are employed. Several piperazine phenothiazines have been esterified at a free hydroxyl group with long-chain fatty acids to produce slowly absorbed and hydrolyzed, long-acting, highly lipophilic prodrugs. *Fluphenazine enanthate* and *decanoate* and *haloperidol decanoate* are available in the United States.

The thioxanthenes also have aliphatic or piperazine substituents. The analog of chlorpromazine among the thioxanthenes is *chlorprothixene*. Piperazine-substituted thioxanthenes include *clopenthixol*, *flupenthixol*, *piflutixol*, and *thiothixene*; they are all potent and effective antipsychotic agents, although only thiothixene is available in the United States. Since thioxanthenes have an olefinic double bond between the central-ring carbon atom at position 10 and the side chain, geometric isomers exist; the *cis* (or α) isomers are the more active.

The phenothiazines and thioxanthenes used in psychiatry have three carbon atoms interposed between position 10 of the central ring and the first amino nitrogen atom of the side chain at this position; the amine is always tertiary. Antihistaminic phenothiazines (*e.g.*, *promethazine*) or strongly anticholinergic phenothiazines (*e.g.*, *ethopropazine*, *diethazine*) have only two carbon atoms separating the amino group from position 10 of the central ring. Metabolic N-desalkylation of the side chain or increasing the size of amino N-alkyl substituents reduces activity.

Another group of tricyclic antipsychotic agents are the *dibenzepines*, containing a seven-member central ring, of which *loxapine* (a dibenzoxazepine) and *clozapine* (a dibenzodiazepine) are available in the United States. They exemplify two growing families of agents. The *loxapine-like family* includes potent and typical neuroleptic agents with prominent antidopaminergic activity (*e.g.*, *clothiapine*, *metiapine*, *loxapine*, *zotapine*, and others). They have an electron-withdrawing moiety at position 2, relatively close to the side-chain nitrogen atoms. The *clozapine-like family* either lacks a ring substituent (*e.g.*, ICI-204,636) or has an electronegative substituent at position 8, away from the side-chain nitrogen atoms (*e.g.*, clozapine, fluperlapine, olanzapine, and others). Clozapine-like agents tend to have low potency, to have a relatively low affinity at most dopamine receptors, and to interact at several other classes of receptors (muscarinic, $5\text{-}HT_2$, α-adrenergic, H_1 histamine, and others). Some are highly effective antipsychotic agents, even in chronically ill patients

Table 18–1
Selected Antipsychotic Drugs: Chemical Structures, Doses and Dosage Forms, and Side Effects*

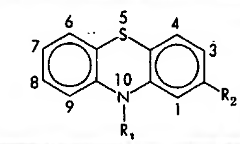
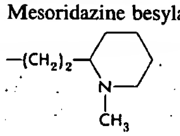
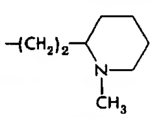
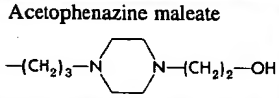
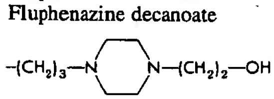
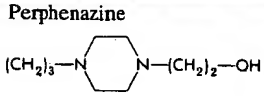
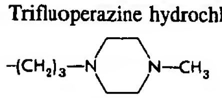
NONPROPRIETARY NAME / TRADE NAME		DOSE AND DOSAGE FORMS †			SIDE EFFECTS		
Phenothiazines 		*Adult Antipsychotic Oral Dose Range—Daily Dosage*		*Single Intramuscular Dose ‡*	*Sedative Effects*	*Extra-pyramidal Effects*	*Hypotensive Effects*
R_1	R_2	Usual, mg	Extreme, § mg	Usual, mg			
Chlorpromazine hydrochloride $—(CH_2)_3—N(CH_3)_2$ THORAZINE, others	$—Cl$	200–800 O, SR, L, I, S	30–2000	25–50	+++	++	IM [illegible] Oral [illegible]
Mesoridazine besylate  SERENTIL	$—S(=O)CH_3$	75–300 O, L, I	30–400	25	+++	+	++
Thioridazine hydrochloride  MELLARIL, MILLAZINE	$—SCH_3$	150–600 O, L	20–800		+++	+	++[illegible]
Acetophenazine maleate  TINDAL	$—COCH_3$	40–120 O	40–400		++	++	+
Fluphenazine hydrochloride Fluphenazine enanthate Fluphenazine decanoate  PERMITIL and PROLIXIN (HYDROCHLORIDES) PROLIXIN (ENANTHATE and DECANOATE)	$—CF_3$	2–20 O, L, I	0.5–30	1.25–2.5 (decanoate or enanthate: 12.5–50 every 1–4 weeks)	+	++++	+
Perphenazine  TRILAFON	$—Cl$	8–32 O, L, I	4–64	5–10	++	++	+
Trifluoperazine hydrochloride  STELAZINE, SUPRAZINE	$—CF_3$	5–20 O, L, I	2–30	1–2	+	+++	+

Table 18–1
Selected Antipsychotic Drugs: Chemical Structures, Doses and Dosage Forms, and Side Effects* (*Continued*)

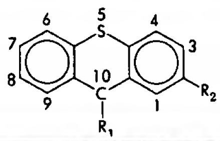
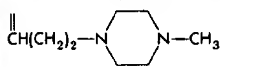
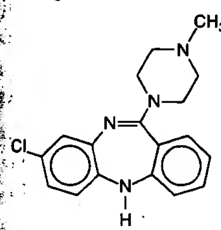
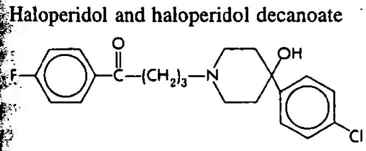
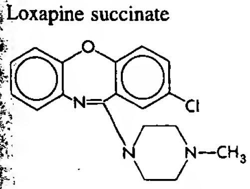
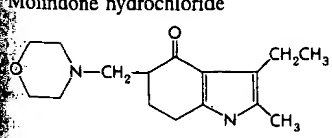
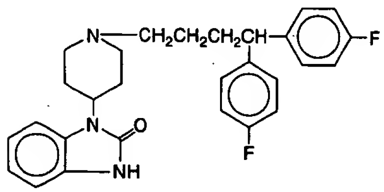
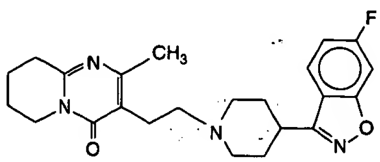
NONPROPRIETARY NAME / TRADE NAME		DOSE AND DOSAGE FORMS †				SIDE EFFECTS		
		Adult Antipsychotic Oral Dose Range—Daily Dosage		*Single Intramuscular Dose ‡*		*Sedative Effects*	*Extra-pyramidal Effects*	*Hypotensive Effects*
Thioxanthenes 								
R₁	R₂	Usual, mg	Extreme, § mg	Usual, mg	Dosage forms			
Chlorprothixene ‖ CH—$(CH_2)_2$—$N(CH_3)_2$ TARACTAN	—Cl	50–400	30–600	25–50	O, L, I	+++	++	++
Thiothixene hydrochloride  NAVANE	—SO_2—$N(CH_3)_2$	5–30	2–30	2–4	O, L, I	+ to ++	+++	++
Other Heterocyclic Compounds								
Clozapine  CLOZARIL		150–450	12.5–900		O	+++	0	+++
Haloperidol and haloperidol decanoate  HALDOL, HALPERON		2–20	1–50	2–5 (haloperidol decanoate: 25–250 every 2–4 weeks)	O, L, I	+	++++	+
Loxapine succinate  LOXITANE		60–100	20–250	12.5–50	O, L, I	+	++	+
Molindone hydrochloride  MOBAN		50–225	15–225		O, L	++	++	+

Table 18–1
Selected Antipsychotic Drugs: Chemical Structures, Doses and Dosage Forms, and Side Effects* *(Continued)*

NONPROPRIETARY NAME	TRADE NAME	DOSE AND DOSAGE FORMS †			SIDE EFFECTS		
Other Heterocyclic Compounds (cont.)							
Pimozide 	ORAP	2–6	1–10	O	+	+++	+
Risperidone 	RISPERDAL	2–8	0.25–16	O	++	++	+++

* Antipsychotic agents for use in children under age 12 years include chlorpromazine, chlorprothixene (> 6 years), thioridazine, and triflupromazine (among agents of low potency); and prochlorperazine and trifluoperazine (> 6 years) (among agents of high potency). Haloperidol (orally) has also been used extensively in children.

† Dosage forms are indicated as follows: I, injection; L, oral liquid; O, oral solid; S, suppository; SR, oral, sustained release; IM, intramuscular.

‡ Except for the enanthate and decanoate forms of fluphenazine and haloperidol decanoate, dosage can be given intramuscularly up to every 6 hours for agitated patients. Haloperidol lactate has been given intravenously; this is experimental.

§ Extreme dosage ranges are occasionally exceeded cautiously and only when other appropriate measures have failed.

Side effects: 0, absent; +, low; ++, moderate; +++, moderately high; ++++, high.

who respond poorly to standard neuroleptics. Their basic and clinical pharmacology has been reviewed by Baldessarini and Frankenburg (1991). Clozapine has stimulated the search for additional, safer, "atypical" agents with antipsychotic activity and a low risk of extrapyramidal neurological side effects.

The *butyrophenone* (phenylbutylpiperidine) neuroleptics include *haloperidol* (Janssen, 1965). Other experimental heterocyclic-substituted phenylbutylpiperidines include the spiperones. Some of these very potent neuroleptics are employed experimentally as radiotracers and to label dopamine D2 receptors for clinical brain scanning (Sedvall, 1992). An analogous compound, *droperidol*, is a very short-acting, highly sedative neuroleptic that is used almost exclusively in anesthesia or in psychiatric emergencies. Additional analogs in the *diphenylbutylpiperidine series* include *fluspirilene, penfluridol*, and *pimozide* (Neumeyer and Booth, 1995). These are potent neuroleptics with prolonged action. In the United States, pimozide is indicated mainly for the treatment of Tourette's syndrome of severe tics and involuntary vocalizations.

Several other classes of heterocyclic compounds have neuroleptic or antipsychotic effects, but too few are available or sufficiently well characterized to permit conclusions regarding structure–activity relationships (*see* Neumeyer and Booth, 1995). These include several indole compounds (notably, *molindone* and *oxypertine*). Another experimental compound, *butaclamol*, is pentacyclic with a dibenzepine core. Its active (dextrorotatory) and inactive enantiomeric forms have been useful in characterizing the stereochemistry of sites of action of neuroleptics at dopamine receptors. A new heterocyclic neuroleptic, *risperidone*, is a *benzisoxazole* with prominent antiserotonergic (5-HT_2) as well as antidopaminergic (D2) activity. Risperidone can be considered a "quantitatively atypical" antipsychotic agent, in that its extrapyramidal neurological side effects are limited if low doses are used (below 6 mg daily). A growing series of heterocyclic neuroleptics are the enantiomeric substituted *benzamides*. These include the gastroenterologic agents *metoclopramide* and *cisapride*, which have antiserotonergic as well as anti-D2 dopaminergic actions. In addition, several benzamides, like the butyrophenones and their congeners, are relatively selective antagonists at central D2 dopamine receptors, and many have neuroleptic-antipsychotic activity. Experimental examples include *emonapride, epidepride, eticlopride, raclopride, remoxipride*, and *sultopride*; *sulpiride* is employed clinically in other countries, mainly as a sedative.

The antipsychotic drugs share many pharmacological effects and therapeutic applications. Chlorpromazine and haloperidol are commonly taken as prototypes for the group. Many antipsychotic drugs, especially chlorpromazine and other agents of low potency, have a prominent sedative effect. This is particularly conspicuous early in treatment, although tolerance to this effect is typical; sedation may not be noticeable when very agitated psychotic patients are treated. Antipsychotic drugs also have antianxiety effects. However, this class of agents is not generally used for such a purpose, largely because of their autonomic and neurological side effects, which paradoxically can include severe anxiety and restlessness (akathisia). The risk of developing extrapyramidal side effects including tardive dyskinesia following long-term administration of antipsychotic drugs makes these agents less desirable than others for the treatment of anxiety.

The term *neuroleptic* was introduced to denote the effects of chlorpromazine and reserpine on psychiatric patients and was intended to contrast the effects of these agents with those of classical CNS depressants. The neuroleptic syndrome involves suppression of spontaneous movements and complex behaviors, while spinal reflexes and unconditioned nociceptive-avoidance behaviors remain intact. In human beings, neuroleptic drugs reduce initiative and interest in the environment, as well as manifestations of emotion or affect. Initially, there may be some slowness in response to external stimuli and drowsiness. However, subjects are easily aroused, can answer direct questions, and retain intact intellectual functions; ataxia, incoordination, or dysarthria do not occur at ordinary doses. Typically, psychotic patients soon become less agitated, and withdrawn or autistic patients sometimes become more responsive and communicative. Aggressive and impulsive behavior diminishes. Gradually (usually over a period of days), psychotic symptoms of hallucinations, delusions, and disorganized or incoherent thinking tend to disappear. Early clinical reports of the effects of chlorpromazine also described neurological effects, including bradykinesia, mild rigidity, some tremor, and subjective restlessness (akathisia), that resemble the signs of Parkinson's disease.

Although the original use of the term *neuroleptic* appears to have encompassed the whole unique syndrome just described and is widely used as a synonym for *antipsychotic*, there is now a tendency to use the term *neuroleptic* to emphasize the more neurological aspects of the syndrome (*i.e.*, the parkinsonian and other extrapyramidal effects). Except for clozapine, all antipsychotic drugs available in the United States also have effects on movement and posture and can thus be called neuroleptic. However, the more general and hopeful term *antipsychotic* is commonly used and may be preferable. Introduction of atypical drugs such as clozapine that are clearly antipsychotic and have little extrapyramidal action has reinforced this trend.

General Psychophysiological and Behavioral Effects. In animals and in human beings, the most prominent observable effects of typical neuroleptic agents are strikingly similar. In low doses, operant behavior is reduced but spinal reflexes are unchanged. Exploratory behavior is diminished, and responses to a variety of stimuli are fewer, slower, and smaller in magnitude, although the ability to discriminate stimuli is retained. Conditioned avoidance behaviors are selectively inhibited, whereas unconditioned escape or avoidance responses are not. Highly reinforcing self-stimulation of the animal brain (typically studied with electrodes placed in the monoamine-rich medial forebrain bundle) is blocked, although the capacity to press the stimulation-inducing lever is not lost. Behavioral activation, stimulated environmentally or pharmacologically, is blocked. Feeding is inhibited. Most neuroleptics block the emesis, hyperactivity, and aggression induced by apomorphine and other dopaminergic agonists. In high doses, most neuroleptic agents induce characteristic cataleptic immobility that allows the animal to be placed in abnormal postures that persist. Muscle tone is increased, and ptosis is typical. The animal appears to be indifferent to most stimuli, although it continues to withdraw from those that are noxious or painful. Many learned tasks still can be performed if sufficient stimulation and motivation are provided. Even very high doses of most neuroleptics do not induce coma, and the lethal dose is extraordinarily high. Many of these effects have been well summarized by Fielding and Lal (1978).

Effects on Motor Activity. Nearly all of the neuroleptic agents used in psychiatry diminish spontaneous motor activity in animals and in human beings. However, one of the more disturbing side effects of these agents in human beings is akathisia, which is manifested by an increase in restless activity that is not readily mimicked by animal behavior. The cataleptic immobility of animals treated with neuroleptics resembles the catatonia seen in some psychotic patients and in a variety of metabolic and neurological disorders affecting the CNS. In human beings, catatonic signs, along with other features of psychotic illnesses,

are sometimes relieved by antipsychotic agents. However, rigidity and bradykinesia, which mimic catatonia, can be induced in patients, especially by large doses of the more potent neuroleptic agents, and reversed by removal of the offending drug or the addition of an antiparkinsonian agent (*see* Fielding and Lal, 1978; Janssen and Van Bever, 1978). Theories concerning the mechanisms underlying these extrapyramidal reactions, as well as descriptions of their clinical presentations and management, are given below.

Effects on Sleep. Antipsychotic drugs have inconsistent effects on sleep patterns, but tend to normalize sleep disturbances characteristic of many psychoses. The ability to prolong and enhance the effect of opioid and hypnotic drugs appears to parallel the sedative rather than the neuroleptic potency of a particular agent. Thus, the more potent neuroleptic agents that do not cause drowsiness also do not enhance hypnosis produced by other drugs.

Effects on Conditioned Responses. Chlorpromazine and other neuroleptics impair the ability of animals to make a conditioned avoidance response to a learned sensory cue that signals the onset of punishing shock avoidable by moving to a safe place in an experimental chamber. Under the influence of small doses of these drugs, animals ignore the warning signal but still attempt to escape once the shock is applied. General CNS depressants affect both avoidance (the conditioned response) and escape (the unconditioned response) to approximately the same extent, but this is seen only with doses of neuroleptics that produce ataxia or hypnosis. Passive avoidance behavior, requiring immobility, also is suppressed by neuroleptic drugs, in contrast to what might be expected in the case of drugs that suppress locomotion.

Since correlations between antipsychotic effectiveness and conditioned avoidance tests are good for many types of neuroleptic agents, they have become an important basis for screening procedures in pharmaceutical psychopharmacology laboratories. Despite their empirical utility and quantitative characteristics, effects on conditioned avoidance have not provided important insights into the basis of antipsychotic effects in human beings. For example, the effects of neuroleptic drugs on conditioned avoidance are subject to tolerance and are blocked by anticholinergic agents, while their clinical antipsychotic actions are not. Moreover, the extraordinarily close correlation between the potencies of drugs in conditioned avoidance tests and their ability to block the behavioral effects of dopaminergic agonists such as amphetamine or apomorphine suggests that such avoidance tests may be selective for drugs with extrapyramidal and other neurological effects. The limited ability of the atypical and perhaps more selective antipsychotic drugs, such as clozapine and sulpiride, to antagonize dopamine agonists or to block conditioned avoidance responses in animal behavioral tests also supports this interpretation. (*See* Fielding and Lal, 1978; Janssen and Van Bever, 1978.)

Effects on Complex Behavior. Antipsychotic drugs impair vigilance in human subjects performing a variety of tasks, such as continuous rotor-pursuit and tapping-speed tests. The drugs produce relatively little impairment of digit–symbol substitution, a test of intellectual functioning. In contrast, barbiturates cause greater impairment in performance in digit–symbol substitution than in continuous performance and other vigilance tests.

Effects on Specific Areas of the Nervous System. The effects of antipsychotic drugs are apparent at all levels in the nervous system. Although the actions underlying the antipsychotic and many of the neurological effects of neuroleptic drugs remain uncertain, theories based on their ability to antagonize the actions of dopamine as a neurotransmitter in the basal ganglia and limbic portions of the forebrain have become most prominent and are supported by a large body of data.

Cerebral Cortex. Since psychosis involves a disorder of higher functions and thought processes, cortical effects of antipsychotic drugs are of great interest. Much attention has been drawn to the effects of neuroleptics on dopaminergic projections to the prefrontal and deep-temporal (limbic) regions of the cerebral cortex and to the relative sparing of these areas from adaptive changes in dopamine metabolism that would suggest tolerance to the actions of neuroleptics. However, little information is available about specific effects on the cortex that sheds light on the mechanisms of action of antipsychotic drugs.

Seizure Threshold. Many neuroleptic drugs can lower the seizure threshold and induce discharge patterns in the EEG that are associated with epileptic seizure disorders. Aliphatic phenothiazines with low potency (such as chlorpromazine) seem particularly able to do this, while the more potent piperazine phenothiazines and thioxanthenes (notably, fluphenazine and thiothixene) seem much less likely to have this effect (Itil, 1978). The butyrophenones have variable and unpredictable effects that cause seizure activity; molindone may have the least activity of this type. Overt seizures associated with the administration of antipsychotic drugs are more likely to be seen in patients who have either a history of epilepsy or a condition that predisposes to seizures. However, clozapine has a clearly dose-related risk of inducing seizures in nonepileptic patients (Baldessarini and Frankenburg, 1991). Neuroleptic agents, especially clozapine and the low-potency phenothiazines and thioxanthenes, should be used with *extreme caution*, if at all, in untreated epileptic patients and in patients undergoing withdrawal from central depressants such as alcohol, barbiturates, or benzodiazepines. Most antipsychotic drugs, especially the piperazines, can be used safely in epileptics if moderate doses are attained gradually and if concomitant anticonvulsant drug therapy is maintained (*see* Chapter 19).

Basal Ganglia. Because the extrapyramidal effects of most clinically used antipsychotic drugs are prominent, a great deal of interest has centered on the actions of these drugs in the basal ganglia, notably the caudate nucleus, putamen, globus pallidus, and allied nuclei, which play a crucial role in the control of posture and the extrapyramidal aspects of movement. Current understanding of the role of a deficiency of dopamine in this region in the pathogenesis of Parkinson's disease, the demonstration that neuroleptic agents act as antagonists of dopamine receptors, and the striking resemblance between the clinical manifestations of Parkinson's disease and the neurological ef-

fects of neuroleptic drugs, all have focused attention on the role of a deficiency of dopaminergic activity in some of the neuroleptic-induced extrapyramidal effects (Baldessarini, 1996a).

The hypothesis that interference with the transmitter function of dopamine in the mammalian forebrain might contribute to the neurological and possibly also the antipsychotic effects of the neuroleptic drugs arose from the observation that neuroleptic drugs consistently increased the concentrations of the metabolites of dopamine but had variable effects on the metabolism of other neurotransmitters. The importance of dopamine also was supported by histochemical studies, which indicated a preferential distribution of dopamine-containing fibers between midbrain and the basal ganglia (notably, the nigroneostriatal tract), and within the hypothalamus (*see* Chapter 12). Other dopamine-containing neurons project from midbrain tegmental nuclei to forebrain regions associated with the limbic system, as well as to temporal and prefrontal cerebral cortical areas closely related to the limbic system. A somewhat simplistic, but attractive, concept arose: many extrapyramidal neurological effects of the antipsychotic drugs might be mediated by antidopaminergic effects in the basal ganglia. Their antipsychotic effects might be mediated by antagonism of dopaminergic neurotransmission in the limbic, mesocortical, and hypothalamic systems.

Antagonism of dopamine-mediated synaptic neurotransmission is an important action of neuroleptic drugs (Carlsson, 1990; Seeman, 1980). Thus, drugs with neuroleptic actions, but not their inactive congeners, initially increase the rate of production of dopamine metabolites, the rate of conversion of the precursor amino acid tyrosine to dihydroxyphenylalanine (DOPA) and its metabolites, and the rate of firing of dopamine-containing cells in the midbrain. These effects usually have been interpreted to represent adaptive responses of neuronal systems that tend to reduce the impact of interrupting synaptic transmission at dopaminergic terminals in the forebrain. Supporting evidence for such an interpretation includes the observation that small doses of neuroleptic drugs block behavioral or neuroendocrine effects of systemically administered or intracerebrally injected dopaminergic agonists. An example is stereotyped gnawing behavior in the rat induced by apomorphine. Many neuroleptic drugs (except the butyrophenones and their congeners and the benzamides) also block the effects of agonists on dopamine-sensitive adenylyl cyclase associated with D1 dopamine receptors in forebrain tissue (Figure 18–1). Atypical antipsychotic drugs such as clozapine are characterized by their low affinity or weak actions in such tests. Whereas the initial effect of neuroleptics is to block D2 receptors and stimulate increased firing and metabolic activity in dopamine neurons, these responses eventually are replaced by diminished activity ("depolarization inactivation"), particularly in the extrapyramidal basal ganglia (Bunney *et al.*, 1987). The timing of these adaptive changes correlates well with the gradual evolution of parkinsonian bradykinesia over days in the clinical application of neuroleptics (Tarsy and Baldessarini, 1986).

Radioligand-binding assays for dopamine receptor subtypes have been used to define more precisely the mechanism of action of neuroleptic agents (*see* Civelli *et al.*, 1993; Seeman, 1980). Estimates of the clinical potency of most types of antipsychotic drugs correlate well with their relative potency *in vitro* to inhibit binding of these ligands to D2 dopamine receptors (*see* Chapter 12). This correlation is obscured to some extent by the tendency of neuroleptics to accumulate in brain tissue to different degrees (Tsuneizumi *et al.*, 1992). Nevertheless, almost all clinically effective antipsychotic agents (with the notable exception of clozapine) have characteristically high affinity for D2 receptors. Although some neuroleptics (especially thioxanthenes and phenothiazines) bind with high affinity to D1 receptors, they block D2 receptors and other D2-like receptors including the D3 and D4 receptor subtypes (Sokoloff *et al.*, 1990; Van Tol *et al.*, 1991). Butyrophenones and congeners (*e.g.*, haloperidol, pimozide, N-methylspiperone) as well as experimental benzamide neuroleptics (*e.g.*, raclopride, remoxipride) have relatively high selectivity as antagonists at D2 and D3 dopamine receptors, with variable D4 affinity. The physiological and clinical consequences of blocking D1 or D5 receptors selectively remain obscure, although experimental benzazepines with such properties, but apparently weak antipsychotic effects, are known (Daly and Waddington, 1992).

So-called atypical antipsychotic agents (with a low risk of extrapyramidal side effects), such as clozapine and other dibenzazepines, have low affinity for D2 receptors and little propensity to produce extrapyramidal side effects. They are, however, active α_1-adrenergic antagonists, as are many other antipsychotic agents (Cohen and Lipinski, 1986). This action may contribute to sedative and hypotensive side effects, or might underlie useful psychotropic effects, although systematic assessment of the psychotropic potential of centrally active anti-α-adrenergic agents is lacking. Many antipsychotic agents also have some affinity for 5-HT_2 serotonin receptors, and this is particularly prominent in the case of clozapine, risperidone, and other investigational D2/5-HT_2 antagonists (Chouinard *et al.*, 1993; Gerlach, 1991; Leysen *et al.*, 1994; Meltzer, 1992; *see* also Chapter 11). This admixture of moderate affinities to several CNS receptor types (including also muscarinic acetylcholine and H_1 histamine receptors) may contribute to the virtually unique pharmacological profile of the atypical antipsychotic agent clozapine (Baldessarini and Frankenburg, 1991). Clozapine also has some selectivity for D4 dopamine receptors; although rare in the basal ganglia, the anatomical and physiological status of D3 and D4 receptors in human brain remains incompletely defined, and their potential as targets for novel antipsychotic agents remains to be demonstrated (Civelli *et al.*, 1993; Gingrich and Caron, 1993; Sokoloff *et al.*, 1990; Van Tol *et al.*, 1991).

Most antipsychotic drugs interfere with the actions of dopamine as a neurotransmitter, particularly at D2 and D2-like receptors. These effects may well account for the diverse extrapyramidal effects of the neuroleptic drugs.

Limbic System. Dopaminergic projections from the midbrain terminate on septal nuclei, the olfactory tubercle, the amygdala, and other structures within the temporal and prefrontal lobes of the cerebrum. Because of the dopamine hypothesis just reviewed, much attention also has been given to the mesolimbic and mesocortical systems as possible sites of mediation of some of the antipsychotic effects of these agents. Speculations about the pathophysiology of the idiopathic psychoses such as schizophrenia have for many years centered around the limbic area. Such speculation has been given indirect encouragement by repeated "natural experiments" that have associated psychotic mental phenomena with lesions of the temporal lobe and other portions of the limbic system (*see* Shapiro, 1993). The finding that D3 receptors are preferentially expressed in limbic areas of the CNS has led to increased ef-

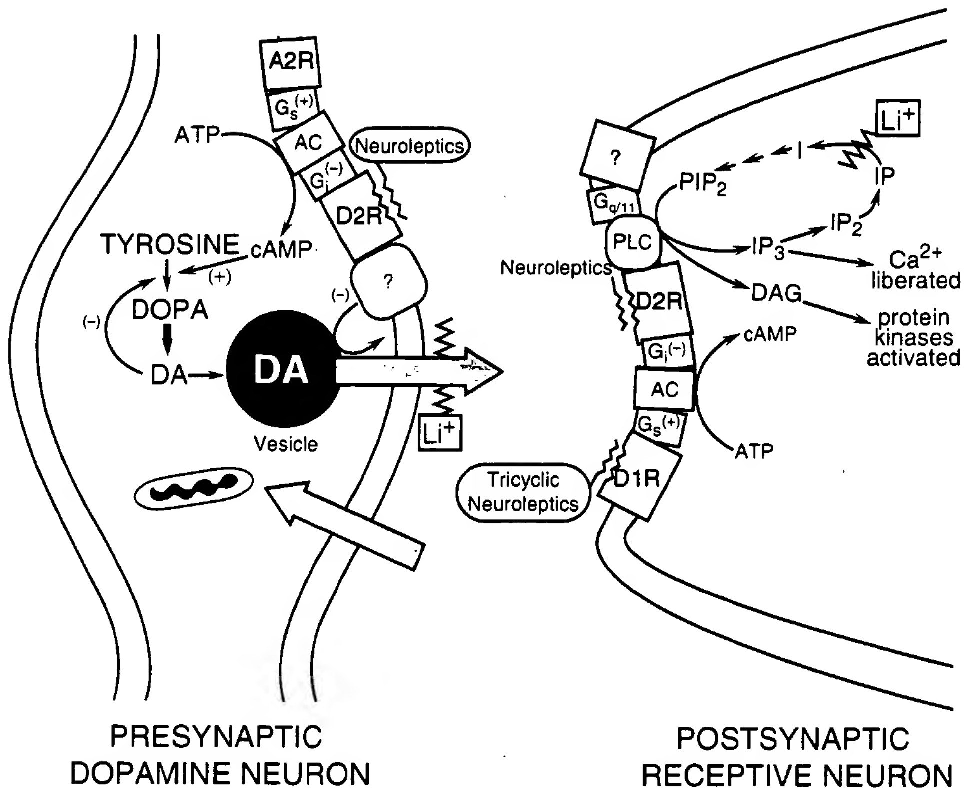


Figure 18–1. Sites of action of neuroleptics and lithium.

In varicosities ("terminals") along terminal arborizations of dopamine (DA) neurons projecting from midbrain to forebrain, tyrosine is oxidized to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase (TH), the rate-limiting step in catecholamine biosynthesis, then decarboxylated to DA by aromatic L-amino acid decarboxylase (AAD) and stored in vesicles. Following exocytotic release (inhibited by lithium) by depolarization in the presence of Ca^{2+}, DA interacts with postsynaptic receptors (R) of D1 and D2 types (and structurally similar but less prevalent D1-like and D2-like receptors), as well as with presynaptic D2 autoreceptors. Inactivation of trans-synaptic communication occurs primarily by active transport ("reuptake") of DA into presynaptic terminals (inhibited by many stimulants), with secondary deamination by mitochondrial monoamine oxidase (MAO). Postsynaptic D1 receptors, through G_s type G proteins, activate adenylyl cyclase (AC) and the conversion of ATP to cyclic AMP (cAMP), while D2 receptors inhibit AC through G_i proteins. D2 receptors also activate receptor-operated K^+ channels and stimulate phospholipase-C (PLC), perhaps *via* the $\beta\gamma$ subunits liberated from activated G_i (*see* Chapter 2), to convert phosphatidylinositol bisphosphate (PIP_2) to inositol trisphosphate (IP_3) and diacylglycerol (DAG), with secondary modulation of Ca^{2+} and protein kinases. Lithium inhibits the phosphatase that liberates inositol (I) from inositol phosphate (IP) and may have other actions. D2 autoreceptors suppress synthesis of DA by diminishing phosphorylation of rate-limiting TH, as well as limiting DA release (possibly through modulation of Ca^{2+} or K^+ currents). In contrast, presynaptic A2 adenosine receptors (A2R) activate AC and, *via* cyclic AMP production, TH activity. Nearly all neuroleptic agents block D2 receptors and autoreceptors; some (particularly thioxanthenes, phenothiazines, and clozapine) also block D1 receptors. Initially in neuroleptic treatment, DA neurons activate and release more DA but, following repeated treatment, they enter a state of physiological depolarization inactivation, with diminished production and release of DA, in addition to continued receptor blockade.

forts tc
a reduc

Ma
pharmac
dopamii
mesolin
tipsychc
includin
(Creese
action:
ample
rolepti
ticholi
charac
called
functio
drugs (s
1978; V
gic agei
ganglia
limbic a
opment
hance tl
extrapyi
Carlssoi

Hypoti
neurol
diated
drugs,
these a
involv
most i
lactin

Th
ably di
fundibu
cleus oi
D2-dop
morphc
dopami
nence a
suppori
hibiting
Jonatha

Cc
ulate pi
for mai
imal ef
neurole
lower d
action
tle tole
lactin,
reversil

forts to identify D3-selective antagonists that might have a reduced tendency to cause extrapyramidal side effects.

Many of the behavioral, neurophysiological, biochemical, and pharmacological findings with regard to the properties of the dopaminergic system of the basal ganglia have been extended to mesolimbic and mesocortical tissue. Certain important effects of antipsychotic drugs are similar in extrapyramidal and limbic regions, including those on ligand-binding assays for dopaminergic receptors (Creese *et al.*, 1978). However, the extrapyramidal and antipsychotic actions of the neuroleptic drugs differ in a number of ways. For example, while several of the acute extrapyramidal effects of neuroleptic drugs tend to diminish or to disappear with time or when anticholinergic drugs are administered concurrently, this is not characteristic of the antipsychotic effects. However, it must be recalled that different dopaminergic systems are not identical, either functionally or in the physiological regulation of their responses to drugs (*see* Bunney *et al.*, 1987; Moore, 1987; Sulser and Robinson, 1978; Wolf and Roth, 1987). For example, whereas anticholinergic agents block the increase in turnover of dopamine in the basal ganglia induced by neuroleptic agents, they seem not to do so in limbic areas containing dopaminergic terminals. Further, the development of tolerance to the effect of antipsychotic drugs to enhance the turnover of dopamine is not as prominent in limbic as in extrapyramidal areas. For further discussions of this topic, *see* Carlsson (1990).

Hypothalamus and Endocrine Systems. In addition to neurological and antipsychotic effects that appear to be mediated in part by antidopaminergic actions of neuroleptic drugs, endocrine changes occur as a result of effects of these agents on the hypothalamus or pituitary that may also involve dopamine. Prominent among these is the ability of most neuroleptic drugs to increase the secretion of prolactin in human beings.

The effect of neuroleptic agents on prolactin secretion is probably due to a blockade of the pituitary actions of the tuberoinfundibular dopaminergic system that projects from the arcuate nucleus of the hypothalamus to the median eminence. The existence of D2-dopaminergic receptors in the anterior pituitary itself, as well as morphological evidence of an intimate relationship between dopamine-containing neurosecretory terminals in the median eminence and the small blood vessels of the hypophyseal portal system, supports the hypothesis that dopamine is the prolactin release–inhibiting hormone known to exist in the hypothalamus (*see* Ben-Jonathan, 1985; *see also* Chapter 55).

Correlations between the potencies of neuroleptic drugs to stimulate prolactin secretion and to cause behavioral effects are excellent for many types of neuroleptics; clozapine is an exception, with minimal effects on prolactin (Rubin, 1987; Sachar, 1978). The effects of neuroleptic drugs on prolactin secretion tend to occur, however, at lower doses than do their antipsychotic effects; this may reflect their action outside the blood–brain barrier in the adenohypophysis. Little tolerance develops to the effect of antipsychotic drugs on prolactin, even after years of treatment. However, the effect is rapidly reversible when the drugs are discontinued (Bitton and Schneider, 1992). This effect of antipsychotic agents is presumed to be responsible for the breast engorgement and galactorrhea that occasionally is associated with their use, sometimes even in male patients given high doses of neuroleptic agents. Because antipsychotic drugs are used chronically and thus cause prolonged hyperprolactinemia, concern arose over their possible contribution to risk of carcinoma of the breast. There is no convincing evidence of such an association (Overall, 1978). Nevertheless, neuroleptic and other agents that stimulate secretion of prolactin should be avoided in patients with established carcinoma of the breast, particularly with metastases. Some neuroleptics reduce secretion of gonadotropins, estrogens, and progestins, possibly contributing to amenorrhea.

The effects of neuroleptics on other hypothalamic neuroendocrine functions are much less well characterized, although it is known that neuroleptics inhibit the release of growth hormone, and chlorpromazine may reduce the secretion of corticotropin-releasing hormone (CRH) that occurs in response to stress. Neuroleptics also interfere with the secretion of pituitary growth hormone. Nevertheless, neuroleptics are poor therapy for acromegaly, and there is no evidence that they retard growth or development of children. In addition, chlorpromazine can decrease secretion of neurohypophyseal hormones. Weight-gain and increased appetite occur with most neuroleptics, particularly those of low potency. Chlorpromazine also may impair glucose tolerance and insulin release to a clinically appreciable degree in some "pre-diabetic" patients (Erle *et al.*, 1977). This effect is not known to occur with other neuroleptics.

In addition to neuroendocrine effects, it is likely that other autonomic effects of antipsychotic drugs may be mediated by the hypothalamus. An important example is the poikilothermic effect of chlorpromazine and other neuroleptic agents, which impairs the body's ability to regulate temperature such that hypo- or hyperthermia may result, depending on the ambient temperature.

Brainstem. Clinical doses of the neuroleptics usually have little effect on respiration. However, vasomotor reflexes mediated by either the hypothalamus or the brainstem are depressed by relatively low doses of chlorpromazine. This effect might occur at many points in the reflex pathway, and the net result is a centrally mediated fall in blood pressure. Even in cases of acute overdosage with suicidal intent, the phenothiazines usually do not cause life-threatening coma or suppression of vital functions; this contributes importantly to their safety.

Chemoreceptor Trigger Zone (CTZ). Most neuroleptics protect against the nausea- and emesis-inducing effects of apomorphine and certain ergot alkaloids, all of which can interact with central dopaminergic receptors in the CTZ of the medulla. The antiemetic effect of most neuroleptics occurs with low doses. Drugs or other stimuli that cause emesis by an action on the nodose ganglion or locally on the gastrointestinal tract are not antagonized by antipsychotic drugs, but potent piperazines and butyrophenones are sometimes effective against nausea caused by vestibular stimulation.

Autonomic Nervous System. Since various antipsychotic agents have antagonistic interactions at peripheral, α-adrenergic, serotonin ($5\text{-}HT_2$), and histamine (H_1) receptors, their effects on the autonomic nervous system are complex and unpredictable. Antihistaminic and antitryptaminergic effects of these agents further complicate the picture. Chlorpromazine has significant α-adrenergic antagonistic activity and can block the pressor effects of norepinephrine. The potent piperazine tricyclic neuroleptics, as well as haloperidol and risperidone, have antipsychotic effects even when used in low doses and show little antiadrenergic activity in patients.

The muscarinic cholinergic blocking effects of antipsychotic drugs are relatively weak, but the blurring of vision commonly experienced with chlorpromazine may be due to an anticholinergic action on the ciliary muscle. Chlorpromazine regularly produces miosis in human beings, which can be due to α-adrenergic blockade. Other phenothiazines can cause mydriasis; this is especially likely to occur with thioridazine, which is the most potent muscarinic antagonist of the group. Chlorpromazine has intermediate antimuscarinic potency but also can cause constipation and decreased gastric secretion and motility. Decreased sweating and salivation are additional manifestations of the anticholinergic effects of the phenothiazines. Acute urinary retention is uncommon, but can occur in males with prostatism. Anticholinergic effects are least frequently caused by the potent neuroleptics, including haloperidol and risperidone. The phenothiazines inhibit ejaculation without interfering with erection. Thioridazine produces this effect with some regularity, sometimes limiting its acceptance by male patients. Attribution of this effect to adrenergic blockade is logical but unsubstantiated, inasmuch as thioridazine is less potent than chlorpromazine in its antiadrenergic effects.

Kidney. Chlorpromazine may have weak diuretic effects in animals and human beings because of a depressant action on the secretion of antidiuretic hormone (ADH), or inhibition of reabsorption of water and electrolytes by a direct action on the renal tubule, or both. The slight fall in blood pressure that occurs with chlorpromazine is not associated with a significant change in glomerular filtration rate; indeed, renal blood flow tends to increase.

Cardiovascular System. The actions of chlorpromazine on the cardiovascular system are complex because the drug produces direct effects on the heart and blood vessels, and also indirect actions through CNS and autonomic reflexes. Chlorpromazine causes mild orthostatic hypotension, systolic blood pressure being affected more than diastolic. Tolerance develops to the hypotensive effect, so that after several weeks of administration pressures return toward normal. However, some degree of orthostatic hypotension may persist indefinitely, especially in elderly patients (*see* Ray *et al.*, 1987). Orthostatic hypotension occurs more frequently with chlorpromazine and thioridazine, and less so with piperazine derivatives, haloperidol, loxapine, molindone, or risperidone.

Chlorpromazine and other phenothiazines with low potency can have a direct negative inotropic action and a quinidine-like antiarrhythmic effect on the heart. ECG changes include prolongation of the Q-T and P-R intervals, blunting of T waves, and depression of the S-T segment. Thioridazine, in particular, causes a high incidence of Q-T and T wave changes and may very rarely produce ventricular arrhythmias and sudden death. These effects are uncommon when potent antipsychotic agents are administered.

Liver. Aside from the hypersensitivity reactions occasionally seen after administration of the antipsychotic drugs, such as an obstructive form of jaundice (*see* below), these agents have no characteristic hepatic effects. The drugs may be used in patients with hepatic disease, but caution is advisable. Since their metabolism may be delayed or modified, they may compromise an already diseased liver.

Miscellaneous Pharmacological Effects. Interactions of antipsychotic drugs with central neurohumors other than dopamine may contribute to their antipsychotic effects or other actions (*see* Baldessarini, 1996b). For example, many neuroleptics enhance the turnover of acetylcholine, especially in the basal ganglia, perhaps secondary to the blockade of dopamine receptors on cholinergic neurons. In addition, as discussed above, there is an inverse relationship between antimuscarinic potency of antipsychotic drugs in the brain and the likelihood of extrapyramidal effects (Snyder and Yamamura, 1977). Although chlorpromazine and a few other low-potency phenothiazines have mild antagonistic actions at receptors for histamine, this effect is not shared by all antipsychotic drugs. Antagonistic interactions also are known to occur at receptors for 5-HT, including those designated as 5-HT_2 in the forebrain. The significance of this effect is not certain, but several antipsychotic agents have been developed with relatively potent and selective antagonistic activity at serotonin 5-HT_2 and D2 dopamine receptors (*e.g.,* amperozide, clozapine, risperidone).

Absorption, Distribution, Fate, and Excretion. Some antipsychotic drugs tend to have erratic and unpredictable patterns of absorption, particularly after oral administration and even when liquid preparations are used. Parenteral (intramuscular) administration increases the bioavailability of active drug by four to ten times. The drugs are highly lipophilic, highly membrane- or protein-bound, and accumulate in the brain, lung, and other tissues with a high blood supply; they also enter the fetal circulation and breast milk. It is virtually impossible (and usually not necessary) to remove these agents by dialysis.

The pharmacokinetics of antipsychotic drugs follows a multiphasic pattern. The usually stated elimination half-lives with respect to total concentrations in plasma are typically 20 to 40 hours, but complex patterns of elimination may occur with some agents, particularly the butyrophenones and their congeners (Cohen *et al.*, 1992). The biological effects of single doses of most neuroleptics usually persist for at least 24 hours; this encourages the common practice of giving the entire daily dose at one time, once the patient has accommodated to the initial side effects of the drug. Elimination from the plasma may be more rapid than from sites of high lipid content and binding, notably in the CNS, but direct pharmacokinetic studies on this issue are few and inconclusive (Sedvall, 1992). Metabolites of some agents have been detected in the urine for as long as several months after administration of the drug has been discontinued. Slow removal of drug may contribute to the typically slow rate of exacerbation of psychosis after stopping drug treatment. Repository ("depot") preparations of esters of neuroleptic drugs are absorbed and eliminated much more slowly than are oral preparations. For example, whereas half of an oral dose of fluphenazine hydrochloride is eliminated in about 20 hours, the elimination of the enanthate or decanoate ester, following a depot intramuscular injection, has a nominal half-life of 2 to 3 or 7 to 10 days, respectively, although the overall clear-

ance of fluphe
perprolactinem
to 8 months (S
The main
drugs are oxid
cally controlle
gation process
are excreted ir
Most oxidize
logically ina
chlorpromaz
lated metab
may contrib
stance, as w
assays of drug
tent antipsych
patic metaboli
and other phe
weeks of treat
ble that altera
responsible. T
minished cap
chotic agents;
rapidly than c

The absorp
the bioavailabili
uid concentrates
concentrations i
cular administr
tabolism in th
measurable co
bioavailability
clinical dose u
trointestinal ab
by food and is
as to whether
tiparkinsonian
neuroleptic age
antipsychotic a
proteins. Typic
bumin. Conce
brain can be m
al., 1992), and
as 20 liters p
plasma include
slower early e
variable values
human brain is
scanning techn
dol from hum
ent half-life in
($t_{1/2}$ > 1 week
Attempts
or its metabol
cessful (*see* B

ance of fluphenazine decanoate and normalization of hyperprolactinemia following repeated dosing can require 6 to 8 months (Sampath *et al.*, 1992).

The main routes of metabolism of the antipsychotic drugs are oxidative processes mediated largely by genetically controlled hepatic microsomal oxidases and conjugation processes. Hydrophilic metabolites of these drugs are excreted in the urine and, to some extent, in the bile. Most oxidized metabolites of antipsychotic drugs are biologically inactive, but a few are not (notably, 7-hydroxychlorpromazine, mesoridazine, and several N-demethylated metabolites of phenothiazines and clozapine) and may contribute to the biological activity of the parent substance, as well as complicate the problem of correlating assays of drug in blood with clinical effects. The less potent antipsychotic drugs may weakly induce their own hepatic metabolism, since concentrations of chlorpromazine and other phenothiazines in blood are lower after several weeks of treatment with the same dosage; it also is possible that alterations of gastrointestinal motility are partially responsible. The fetus, the infant, and the elderly have diminished capacity to metabolize and eliminate antipsychotic agents; children tend to metabolize these drugs more rapidly than do adults (Popper, 1987).

The absorption of tablets of chlorpromazine is erratic, although the bioavailability seems to be increased somewhat by the use of liquid concentrates, as is true for many of the antipsychotic agents. Peak concentrations in plasma are attained within 2 to 4 hours. Intramuscular administration of the drug avoids much of the first-pass metabolism in the liver (and possibly also the gut) and provides measurable concentrations in plasma within 15 to 30 minutes; bioavailability may be increased up to tenfold with injections, but the clinical dose usually is decreased by three- to fourfold. The gastrointestinal absorption of chlorpromazine is modified unpredictably by food and is probably decreased by antacids. There is controversy as to whether the concurrent administration of anticholinergic antiparkinsonian agents diminishes the intestinal absorption of some neuroleptic agents (Simpson *et al.*, 1980). Chlorpromazine and other antipsychotic agents bind significantly to membranes and to plasma proteins. Typically, over 85% of the drug in plasma is bound to albumin. Concentrations of some neuroleptics (*e.g.*, haloperidol) in brain can be more than ten times those in the blood (Tsuneizumi *et al.*, 1992), and their apparent volume of distribution may be as high as 20 liters per kilogram. Disappearance of chlorpromazine from plasma includes a rapid distribution phase ($t_{1/2}$ about 2 hours) and a slower early elimination phase ($t_{1/2}$ about 30 hours), but markedly variable values have been reported; the half-life of elimination from human brain is not known but may be determined using modern brain-scanning technologies (Sedvall, 1992). The elimination of haloperidol from human plasma is not a log-linear function, and the apparent half-life increases with time: very slow terminal-elimination rates ($t_{1/2}$ > 1 week) may ultimately be attained (Cohen *et al.*, 1992).

Attempts to correlate plasma concentrations of chlorpromazine or its metabolites with clinical responses have not been very successful (*see* Baldessarini *et al.*, 1988; Cooper *et al.*, 1976). Studies have revealed wide variations (at least tenfold) in plasma concentrations among individuals. Although it appears that plasma concentrations of chlorpromazine below 30 ng/ml are not likely to produce an adequate antipsychotic response and that levels above 750 ng/ml are likely to be associated with unacceptable toxicity (*see* Rivera-Calimlim and Hershey, 1984), it is not yet possible to state with confidence the concentrations in plasma that are likely to be associated with optimal clinical responses.

At least 10 or 12 metabolites of chlorpromazine occur in human beings in appreciable quantities (Morselli, 1977). Quantitatively, the most important of these are nor$_2$-chlorpromazine (doubly demethylated), chlorophenothiazine (removal of the entire side chain), methoxy and hydroxy products, and glucuronide conjugates of the hydroxylated compounds. In the urine, 7-hydroxylated and dealkylated (nor$_2$) metabolites and their conjugates predominate.

The pharmacokinetics and metabolism of thioridazine and fluphenazine are similar to those of chlorpromazine, but the strong anticholinergic action of thioridazine on the gut may modify its own absorption. Major metabolites of thioridazine and fluphenazine include N-demethylated, ring-hydroxylated, and S-oxidized products (Neumeyer and Booth, 1995). Concentrations of thioridazine in plasma are relatively high (hundreds of nanograms per milliliter), possibly because of its relative hydrophilicity, and it is suspected that mesoridazine is an important contributor to the neuroleptic activity of thioridazine.

The biotransformation of the thioxanthenes is similar to that of the phenothiazines, except that metabolism to sulfoxides is common and ring-hydroxylated products are uncommon. Piperazine derivatives of the phenothiazines and thioxanthenes also are handled much like chlorpromazine, although metabolism of the piperidine ring itself occurs. Haloperidol and other butyrophenones are metabolized primarily by an N-dealkylation reaction; the resultant fragments can be conjugated with glucuronic acid. It is believed that all of the metabolites of haloperidol are inactive (Forsman and Öhman, 1974), with the possible exception of a hydroxylated product formed by reduction of the keto moiety that may be reoxidized to haloperidol (Korpi *et al.*, 1983). Typical plasma concentrations of haloperidol encountered clinically are about 5 to 20 ng/ml, and these correspond to 80% to 90% occupancy of D2 dopamine receptors in human basal ganglia, as demonstrated by positron-emission tomographic (PET) brain scanning (Baldessarini *et al.*, 1988; Wolkin *et al.* 1989).

Tolerance and Physical Dependence. The antipsychotic drugs are not addicting, as the term is defined in Chapter 24. However, some degree of physical dependence may occur, with malaise and difficulty in sleeping developing several days after abrupt discontinuation.

Tolerance usually develops to the sedative effects of neuroleptics over a period of days or weeks. Tolerance to antipsychotic drugs and cross-tolerance among the agents also are demonstrable in behavioral and biochemical experiments in animals, particularly those directed toward evaluation of the blockade of dopaminergic receptors in the basal ganglia (*see* Baldessarini and Tarsy, 1979). This form of tolerance may be less prominent in limbic and cortical areas of the forebrain. One correlate of tolerance in forebrain dopaminergic systems is the development of disuse supersensitivity of those systems, probably mediated by changes in the receptors for the neurotransmitter. This mechanism may underlie the clinical phenomenon of withdrawal-emergent dyskinesias (choreoathetosis on abrupt discontinuation of antipsychotic agents, especially following prolonged use of high doses of potent agents) (Baldessarini *et al.*, 1980). Al-

though cross-tolerance for some effects may occur among neuroleptic drugs, clinical problems occur in making rapid changes from high doses of one type of agent to another; sedation, hypotension, and other autonomic effects or acute extrapyramidal reactions can result.

Preparations and Dosage. Because the number of agents with known neuroleptic or antipsychotic effects is large, Table 18–1 summarizes only those that are currently marketed in the United States. Excluded are a few available agents, such as promazine hydrochloride (SPARINE) and reserpine and other rauwolfia alkaloids, that have inferior antipsychotic effects or that are no longer commonly used for psychiatric patients. Prochlorperazine (COMPAZINE) has questionable utility as an antipsychotic agent and frequently produces acute extrapyramidal reactions; it is thus not commonly employed in psychiatry, although it is used as an antiemetic. Thiethylperazine (TORECAN), which is currently marketed only as an antiemetic, is a potent dopaminergic antagonist with many neuroleptic-like properties; at high doses it may be an efficacious antipsychotic agent (Rotrosen *et al.*, 1978). The United States has been slow to accept many psychotropic agents that are in common use in other countries; many more thioxanthenes, butyrophenones, diphenylbutylpiperidines, benzamides, and long-acting repository preparations of neuroleptic agents are available in other countries.

Toxic Reactions and Side Effects. The antipsychotic drugs have a high therapeutic index and are remarkably safe agents. Furthermore, most phenothiazines have a relatively flat dose–response curve and can be used over a wide range of dosages. Although occasional deaths from overdosage have been reported, this is rare if the patient is given medical care and if an overdosage is not complicated by the concurrent ingestion of alcohol or other drugs. Based on animal data, the therapeutic index is lowest for thioridazine and chlorpromazine and is high for the more potent agents (Janssen and Van Bever, 1978). Adult patients have survived doses of chlorpromazine up to 10 g, and deaths from an overdose of haloperidol alone appear to be unknown.

Side effects are often extensions of the many pharmacological actions of these drugs. The most important are those on the CNS, cardiovascular system, autonomic nervous system, and endocrine functions. The extrapyramidal effects, which are of great importance, are discussed in detail below. Other dangerous effects are seizures, agranulocytosis, and pigmentary degeneration of the retina, all of which are rare (*see* below).

Therapeutic doses of phenothiazines may cause faintness, palpitation, and anticholinergic effects including nasal stuffiness, dry mouth, blurred vision, constipation, and, in males with prostatism, urinary retention. The most troublesome cardiovascular side effect is orthostatic hypotension, which may result in syncope. A fall in blood pressure is most likely to occur from administration of the phenothiazines with aliphatic side chains. Congeners of the piperazine type, as well as other potent neuroleptic agents, produce less hypotension.

Neurological Side Effects. A variety of neurological syndromes, involving particularly the extrapyramidal motor system, occur following the use of almost all antipsychotic drugs. These reactions are particularly prominent during treatment with the high-potency agents (tricyclic piperazines and butyrophenones). There is less likelihood of acute extrapyramidal side effects with clozapine, thioridazine, or low doses of risperidone. The neurological effects associated with antipsychotic drugs have been reviewed in detail (Baldessarini *et al.*, 1980; Baldessarini, 1984; Kane *et al.*, 1992; Tarsy and Baldessarini, 1986).

Six varieties of neurological syndromes are characteristic of antipsychotic drugs. Four of these (acute dystonia, akathisia, parkinsonism, and the rare neuroleptic malignant syndrome) usually appear soon after administration of the drug, and two (rare perioral tremor and tardive dyskinesias or dystonias) are late-appearing syndromes that occur following prolonged treatment. The clinical features of these syndromes and guidelines for their management are summarized in Table 18–2.

Acute dystonic reactions are not uncommonly seen with the initiation of antipsychotic drug therapy, particularly with agents of high potency, and may present as facial grimacing, torticollis, or oculogyric crisis. These syndromes may be mistaken for hysterical reactions or seizures, but they respond dramatically to parenteral administration of anticholinergic antiparkinsonian drugs. Oral administration of anticholinergic agents also can prevent dystonia, particularly in young male patients who have been given a high-potency neuroleptic drug (Arana *et al.*, 1988). Although treated readily, acute dystonic reactions are terrifying to patients; sudden death has occurred in rare instances, perhaps due to the impaired respiration caused by dystonia of pharyngeal, laryngeal, and other muscles.

Akathisia refers to strong subjective feelings of distress or discomfort, often referred to the legs, as well as to a compelling need to be in constant movement rather than to follow any specific movement pattern. Patients feel that they must get up and walk or continuously move about and may be unable to keep this tendency under control. Akathisia often is mistaken for agitation in psychotic patients; the distinction is critical, since agitation might be treated with an increase in dosage. Because the response of akathisia to antiparkinsonian drugs is frequently unsatisfactory, treatment typically requires reduction of antipsychotic drug dosage. Antianxiety agents or moderate doses of propranolol may be beneficial (Lipinski *et al.*, 1984). This common syndrome is frequently not diagnosed and often interferes with the acceptance of neuroleptic treatment.

A *parkinsonian syndrome* that may be indistinguishable from idiopathic parkinsonism commonly develops gradually during administration of antipsychotic drugs. Its incidence varies with different agents (*see* Table 18–2). Clinically, there is a generalized slowing of volitional movement (akinesia) with mask facies and a reduction in arm movements. The syndrome characteristically evolves gradually over days to weeks. The most noticeable signs are rigidity and tremor at rest, especially involving the upper extremities. "Pill-rolling" movements may be seen, although they are not as prominent in neuroleptic-induced as in idiopathic parkinsonism. Parkinsonian side effects may be mistaken for depression, since the

Neurological Sid

REACTION

Acute dystonia

Akathisia

Parkinsonism

Neuroleptic malignant syr drome

Perioral tremc ("rabbit" syndrome)

Tardive dyski

* Many drugs h ride, 25 or the same a
† For details re;
‡ Propranolol oi
§ Despite the r bromocrip

flat facial expi depression. Tl parkinsonian (see Chapter risk of induci

A rare d very severe f

Neurological Side Effects of Neuroleptic Drugs

REACTION	FEATURES	TIME OF MAXIMAL RISK	PROPOSED MECHANISM	TREATMENT
Acute dystonia	Spasm of muscles of tongue, face, neck, back; may mimic seizures; *not* hysteria	1 to 5 days	Unknown	Antiparkinsonian agents are diagnostic and curative*
Akathisia	Motor restlessness; *not* anxiety or "agitation"	5 to 60 days	Unknown	Reduce dose or change drug: antiparkinsonian agents,† benzodiazepines or propranolol ‡ may help
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait	5 to 30 days	Antagonism of dopamine	Antiparkinsonian agents helpful †
Neuroleptic malignant syndrome	Catatonia, stupor, fever, unstable blood pressure, myoglobinemia; can be fatal	Weeks; can persist for days after stopping neuroleptic	Antagonism of dopamine may contribute	Stop neuroleptic immediately: dantrolene or bromocriptine§ may help: antiparkinsonian agents not effective
Perioral tremor ("rabbit" syndrome)	Perioral tremor (may be a late variant of parkinsonism)	After months or years of treatment	Unknown	Antiparkinsonian agents often help †
Tardive dyskinesia	Oral-facial dyskinesia; widespread choreoathetosis or dystonia	After months or years of treatment (worse on withdrawal)	Excess function of dopamine hypothesized	Prevention crucial; treatment unsatisfactory

* Many drugs have been claimed to be helpful for acute dystonia. Among the most commonly employed treatments are diphenhydramine hydrochloride, 25 or 50 mg intramuscularly, or benztropine mesylate, 1 or 2 mg intramuscularly or slowly intravenously, followed by oral medication with the same agent for a period of days to perhaps several weeks thereafter.

† For details regarding the use of oral antiparkinsonian agents, *see* the text and Chapter 22.

‡ Propranolol often is effective in relatively low doses (20–80 mg per day). Selective β_1-adrenergic receptor antagonists are less effective.

§ Despite the response to dantrolene, there is no evidence of an abnormality of Ca^{2+} transport in skeletal muscle; with lingering neuroleptic effects, bromocriptine may be tolerated in large doses (10–40 mg per day).

flat facial expression and retarded movements may resemble signs of depression. This reaction usually is managed by use of either antiparkinsonian agents with anticholinergic properties or amantadine (see Chapter 22); the use of levodopa or bromocriptine incurs the risk of inducing agitation and worsening the psychotic illness.

A rare disorder, *neuroleptic malignant syndrome*, resembles a very severe form of parkinsonism with catatonia, fluctuations in the intensity of coarse tremor, signs of autonomic instability (labile pulse and blood pressure, hyperthermia), stupor, elevation of creatine kinase in plasma, and sometimes myoglobinemia. In its most severe form, this syndrome may persist for more than a week after stopping the offending agent. Because mortality is high (over 10%), immediate medical attention is required. This reaction has been associated with various types of neuroleptics, but its prevalence may be greater

when relatively high doses of the more potent agents are used, especially when they are administered parenterally. Aside from immediate cessation of neuroleptic treatment and provision of supportive care, specific treatment is unsatisfactory; administration of dantrolene or the dopaminergic agonist bromocriptine may be helpful (Addonizio *et al.,* 1987; Pearlman, 1986). Although dantrolene also is used to manage the syndrome of malignant hyperthermia induced by general anesthetics, the neuroleptic-induced form of catatonia and hyperthermia is probably not associated with a defect in Ca^{2+} metabolism in skeletal muscle (*see* Chapter 14).

A rare movement disorder that can appear late in the treatment of chronically ill patients with antipsychotic agents is *perioral tremor,* often referred to as the "rabbit syndrome" (Jus *et al.,* 1974) because of the peculiar movements that characterize this condition. While sometimes categorized with other tardive (late or slowly evolving) dyskinesias, this term is usually reserved for choreoathetotic or dystonic reactions that develop after prolonged therapy. The "rabbit syndrome," in fact, shares many features with parkinsonism, because the tremor has a frequency of about 5 to 7 Hz and there is a favorable response to anticholinergic agents and to the removal of the offending agent.

Tardive dyskinesia is a late-appearing neurological syndrome (or syndromes) associated with the use of neuroleptic drugs. It occurs more frequently in older patients, and risk may be greater in patients with mood disorders than in those with schizophrenia. Prevalence averages 15% to 25% in chronically psychotic populations, with an annual incidence of 3% to 5% and a somewhat smaller annual rate of spontaneous remission, even with continued neuroleptic treatment. The risk is much lower with clozapine, but that of other recently developed atypical antipsychotic agents is not known. Tardive dyskinesia is characterized by stereotyped, repetitive, painless, involuntary, quick choreiform (ticlike) movements of the face, eyelids (blinks or spasm), mouth (grimaces), tongue, extremities, or trunk. There are varying degrees of slower athetosis (twisting movements) and sustained dystonic postures, which are more common in young men and may be disabling. Late (tardive) emergence of possibly related disorders marked mainly by dystonia or akathisia (restlessness) also are seen. These movements all disappear in sleep (as in many other extrapyramidal syndromes), vary in intensity over time, and are dependent on the level of arousal or emotional distress. Although tardive dyskinetic movements can be suppressed partially by use of a potent neuroleptic, and perhaps with a dopamine-depleting agent such as reserpine or tetrabenazine, such interventions are reserved for compellingly severe dyskinesia, particularly with continuing psychosis. Some dyskinetic patients, typically those with dystonic features, may benefit from use of clozapine, with which the risk of tardive dyskinesia is very low. Symptoms sometimes persist indefinitely after discontinuation of neuroleptic medication; more often, they diminish or disappear gradually over months of follow-up, especially in younger patients (Gardos *et al.,* 1994; Morgenstern and Glazer, 1993). Antiparkinsonism agents typically have little effect on or may exacerbate tardive dyskinesia and other forms of choreoathetosis, such as in Huntington's disease, and no adequate treatment has yet been devised (Dabiri *et al.,* 1994).

There is no established neuropathology in tardive dyskinesia, and its pathophysiological basis remains obscure. It has been hypothesized that compensatory increases in the function of dopamine as a neurotransmitter in the basal ganglia may be involved. This idea is supported by the dissimilarities of therapeutic responses in patients with Parkinson's disease and those with tardive dyskinesia, and by the similarities in responses of patients with other choreoathetotic dyskinesias such as Huntington's disease. Thus, antidopaminergic drugs tend to suppress the manifestations of tardive dyskinesia or Huntington's disease, while dopaminergic agonists worsen these conditions; in contrast to parkinsonism, antimuscarinic agents tend to worsen tardive dyskinesia, but cholinergic agents usually are ineffective. Because supersensitivity to dopaminergic agonists tends not to persist for more than a few weeks after exposure to antagonists of the transmitter, this phenomenon is most likely to play a role in variants of tardive dyskinesia that resolve rapidly; these usually are referred to as *withdrawal-emergent dyskinesias.* The theoretical and clinical aspects of this problem have been reviewed in detail elsewhere (Baldessarini *et al.,* 1980; Kane *et al.,* 1992; Tarsy and Baldessarini, 1986).

It is important to prevent the neurological syndromes that complicate the use of antipsychotic drugs. Certain therapeutic guidelines should be followed. Routine use of antiparkinsonian agents in an attempt to avoid early extrapyramidal reactions usually is unnecessary and adds complexity, side effects, and expense to the treatment regimen. Antiparkinsonian agents are best reserved for cases of overt extrapyramidal reactions that respond favorably to such intervention. The need for such agents for the treatment of acute dystonic reactions ordinarily diminishes with time, but parkinsonism and akathisia tend to persist. The thoughtful and conservative use of antipsychotic drugs in patients with chronic or frequently recurrent psychotic disorders almost certainly can reduce the risk of tardive dyskinesia. Although reduction of the dose of an antipsychotic agent is the best way to minimize its neurological side effects, this may not be practical in a patient with uncontrollable psychotic illness. The best preventive practice is to use the minimum effective dose of an antipsychotic drug for long-term therapy and to discontinue treatment as soon as it seems reasonable to do so or if a satisfactory response cannot be obtained. The use of clozapine and other novel antipsychotic agents with a low risk of inducing extrapyramidal side effects represents an alternative for some patients, particularly those with continuing psychotic symptoms plus dyskinesia (Baldessarini and Frankenburg, 1991). A high risk of agranulocytosis exists with clozapine. This leads to the current requirement of a weekly leukocyte count to minimize this risk.

Jaundice. Jaundice was observed in patients shortly after the introduction of chlorpromazine. Commonly occurring during the second to fourth week of therapy, the jaundice is generally mild, and pruritus is rare. The reaction is probably a manifestation of hypersensitivity, because eosinophilic infiltration of the liver as well as eosinophilia occur, and there is no correlation with dose. Desensitization to chlorpromazine may occur with repeated administration, and jaundice may or may not recur if the same neuroleptic agent is given again. When the psychiatric disorder calls for uninterrupted drug therapy for a patient with neuroleptic-induced jaundice, it is probably safest to use low doses of a potent, dissimilar agent.

Blood Dyscrasias. Mild leukocytosis, leukopenia, and eosinophilia occasionally occur with antipsychotic medications, particularly with clozapine and less often with low-potency phenothiazines. It is difficult to determine whether a leukopenia occurring during the administration of a phenothiazine is a forewarning of impending agranulocytosis. This serious but rare complication occurs in not more than 1 in 10,000 patients receiving chlorpromazine or other low-potency agents other than clozapine; it usually appears within the first 8 to 12 weeks of treatment (Alvir *et al.,* 1993). Suppression of the bone marrow or, less commonly, agranulocytosis has been associated particularly with the use of clozapine; the incidence approaches 1%

within several months of treatment, independent of dose, and close monitoring of the patient is required for its safe use. Because the onset of blood dyscrasia may be sudden, the appearance of fever, malaise, or apparent upper respiratory infection in a patient being treated with an antipsychotic drug should be followed immediately by a complete blood count. Risk of agranulocytosis has been greatly reduced, though not eliminated, by routine weekly white blood cell counts in patients being treated with clozapine.

Skin Reactions. Dermatological reactions to the phenothiazines are common. Urticaria or dermatitis occurs in about 5% of patients receiving chlorpromazine. Several types of skin disorders may occur. Hypersensitivity reactions that may be urticarial, maculopapular, petechial, or edematous usually occur between the first and eighth week of treatment. The skin clears following discontinuation of the drug and may remain so even if drug therapy is reinstituted. Contact dermatitis may occur in personnel who handle chlorpromazine, and there may be a degree of cross-sensitivity to the other phenothiazines. Photosensitivity occurs that resembles severe sunburn. An effective sunscreen preparation should be prescribed for outpatients being treated with phenothiazines during the summer. Gray-blue pigmentation induced by long-term administration of low-potency phenothiazines in high doses is rare with current practices.

Epithelial keratopathy often is observed in patients on long-term therapy with chlorpromazine, and opacities in the cornea and in the lens of the eye also have been noted. In extreme cases, deposits in the lens may impair vision. Active treatment of this condition (*e.g.*, with penicillamine) has not been especially helpful, and the deposits tend to disappear spontaneously, although slowly, following discontinuation of drug administration. Pigmentary retinopathy has been reported, particularly following doses of thioridazine in excess of 1000 mg per day; a maximim daily dose of 800 mg currently is recommended.

Interactions with Other Drugs. The phenothiazines and thioxanthenes, especially those of low potency, affect the actions of a number of other drugs, sometimes with important clinical consequences (*see* Goff and Baldessarini, 1993). Chlorpromazine originally was introduced to potentiate central depressants in anesthesiology. Such drugs can strongly potentiate sedatives and analgesics prescribed for medical purposes, as well as alcohol, nonprescription sedatives and hypnotics, antihistamines, and cold remedies. Chlorpromazine increases the miotic and sedative effects of morphine and may increase its analgesic actions. Furthermore, the drug markedly increases the respiratory depression produced by meperidine and can be expected to have similar effects when administered concurrently with other opioids. Obviously, neuroleptic drugs inhibit the actions of direct dopaminergic agonists and of levodopa.

Other interactive effects can be manifest on the cardiovascular system. Chlorpromazine and some other antipsychotic drugs, as well as their N-demethylated metabolites, may block the antihypertensive effects of guanethidine, probably by blocking its uptake into sympathetic nerves. The more potent antipsychotic agents as well as molindone are less likely to cause this effect. Low-potency phenothiazines can promote postural hypotension, possibly due to their α-adrenergic blocking properties. Thus, the interaction between phenothiazines and antihypertensive agents can be unpredictable.

Thioridazine may partially nullify the inotropic effect of digitalis by its quinidine-like action, which can cause myocardial depression, decreased efficiency of repolarization, and increased risk of tachyarrhythmias. The antimuscarinic action of clozapine and thioridazine can cause tachycardia and enhance the peripheral and central effects (confusion, delirium) of other anticholinergic agents, such as the tricyclic antidepressants and antiparkinsonian agents.

Sedatives or anticonvulsants (*e.g.*, carbamazepine, phenobarbital, phenytoin, but not valproate) that induce microsomal drug-metabolizing enzymes can enhance the metabolism of antipsychotic agents, sometimes with significant clinical consequences. Conversely, serotonin reuptake inhibitors including fluoxetine (*see* Chapter 11) compete for hepatic oxidases and can elevate circulating levels of neuroleptics (Goff and Baldessarini, 1993).

DRUG TREATMENT OF PSYCHOSES

The antipsychotic drugs are not specific for the type of psychosis to be treated. They are clearly effective in acute psychoses of unknown etiology, including mania, acute idiopathic psychoses, and acute exacerbations of schizophrenia; the greatest amount of controlled clinical data exists for the acute and chronic phases of schizophrenia. In addition, antipsychotic drugs are used empirically in many other disorders in which psychotic symptoms and severe agitation are prominent.

The fact that phenothiazines and other neuroleptic agents are indeed antipsychotic was slow to gain acceptance. However, many clinical trials and four decades of clinical experience have established that these agents are effective and that they are superior to agents such as the benzodiazepines or to alternatives such as electroconvulsive shock or other medical or psychological therapies (*see* Baldessarini, 1984, 1996b). The "target" symptoms for which the neuroleptic agents seem to be especially effective include tension, hyperactivity, combativeness, hostility, hallucinations, acute delusions, insomnia, anorexia, poor self-care, negativism, and sometimes withdrawal and seclusiveness; less likely are improvements in insight, judgment, memory, and orientation. The most favorable prognosis is for patients with acute illnesses of brief duration who have had relatively healthy personalities prior to the illness.

Despite the great success of the use of antipsychotic drugs, their use alone does not constitute optimal care of psychotic patients. The acute care, protection, and support of acutely psychotic patients, as well as mastery of tech-

niques employed in their long-term care and rehabilitation, are important medical skills. Detailed reviews of the clinical use of antipsychotic drugs are available (Baldessarini, 1984, 1996b; Janicak *et al.*, 1993).

No one drug or combination of drugs has a selective effect on a particular symptom complex in groups of psychotic patients: although individual patients may appear to do better with one agent than another, this can be determined only by trial and error. The concept that certain agents are specifically effective against "negative" symptoms in psychotic disorders remains controversial and rather speculative. Generally, "positive" (psychotic thinking, delusions, agitated turmoil, hallucinations) and "negative" (apathy, emotional withdrawal, lack of social interaction) symptoms tend to respond, or not respond, together. This trend is well documented with typical as well as atypical antipsychotic agents. It is clear that clozapine, at least, induces less bradykinesia and other parkinsonian effects than do typical neuroleptics. This is sometimes interpreted clinically as a beneficial effect on impoverished affective responsiveness. The powerful sedating action of clozapine, however, can work in the opposite direction. It is important to simplify the treatment regimen and to ensure that the patient is receiving the drug. In cases of suspected severe and dangerous noncompliance or with failure of oral treatment, the patient can be treated with injections of fluphenazine decanoate, haloperidol decanoate, or other long-acting preparations. Since delusional paranoid patients frequently believe that the medicine is "poison," they are often given long-acting injectable preparations.

Because the choice of an antipsychotic drug cannot be made on the basis of anticipated therapeutic effect, the selection of a particular medication for treatment often depends on side effects. If a patient has responded well to a drug in the past, it probably should be used again. If the patient has a history of cardiovascular disease or stroke and the threat from hypotension is serious, a potent neuroleptic should be used in the smallest dose that is effective (*see* Table 18–1). If it seems important to minimize the risk of acute extrapyramidal symptoms, thioridazine or clozapine or a low dose of risperidone should be considered. If the patient would be seriously discomforted by interference with ejaculation or if there are serious risks of cardiovascular or other autonomic toxicity, low doses of a potent neuroleptic might be preferred. If sedative effects are undesirable, a potent agent is preferable. Small doses of antipsychotic drugs of high or moderate potency may be safest in the elderly. If the patient has compromised hepatic function or if there is a potential threat of jaundice, low doses of a high-potency agent may be used. The physician's experience with a particular drug may outweigh all other considerations. Skill in the use of antipsychotic drugs depends on selection of an adequate but not excessive dose, knowledge of what to expect, and judgment as to when to stop therapy or change drugs.

Some patients do not respond satisfactorily to antipsychotic drug treatment, and many chronically disorganized schizophrenic patients, while helped during periods of acute exacerbation of their disease, may show unsatisfactory responses between the more acute phases of illness. The individual nonresponder cannot be identified beforehand with certainty, and a small subgroup of patients does poorly or sometimes even becomes worse on medication. If a patient does not improve after a course of adequate treatment and fails to respond to another drug given in adequate dosage, the diagnosis should be reevaluated.

Usually 2 to 3 weeks or more are required to demonstrate obvious positive effects in hospitalized schizophrenics. Maximum benefit in chronically psychotic patients may require 6 weeks to 6 months. In contrast, improvement of some acutely psychotic patients can be seen within 48 hours. Aggressive dosing or parenteral administration of an antipsychotic drug at the start of an acute psychosis has not been found to increase the rate of appearance of therapeutic responses (Baldessarini *et al.*, 1988). Sedative or anxiolytic agents, such as the potent benzodiazepines, can be used for brief periods during the initiation of therapy with neuroleptic drugs; they are not effective in the long-term treatment of chronically psychotic and, especially, schizophrenic patients. After the initial response, drugs usually are used in conjunction with psychological, supportive, and rehabilitative treatments.

There is no convincing evidence that combinations of antipsychotic drugs offer any advantage. A combination of an antipsychotic drug and an antidepressant may be useful in some cases, especially in depressed psychotic patients or in cases of agitated major depression with psychotic features. However, the suggestion that a tricyclic antidepressant or a stimulant can reduce apathy and withdrawal in schizophrenia has not been proven, and the proposal that clozapine, risperidone, diphenylbutylpiperidines, benzamides, or other newer agents are uniquely valuable against such "negative" symptoms of schizophrenia has not been universally accepted.

Optimal dosage of antipsychotic drugs requires individualization to determine doses that are effective, well-tolerated, and accepted by a patient. Dose–response relationships for the antipsychotic effects and the neurological side effects overlap, and an end-point of a desired therapeutic response can be difficult to determine. The typical effective dose of chlorpromazine is approximately 300 to 500 mg daily; 5 to 15 mg of haloperidol daily usually produces clearly apparent antipsychotic effects. Doses of as little as 50 to 200 mg of chlorpromazine per day (or 2 to 6 mg of haloperidol or fluphenazine per day) may be effective and be better tolerated by many patients, especially after the initial improvement of acute symptoms (Baldessarini *et al.*, 1988). Careful observation of the patient's changing response is the best guide to dosage.

In the treatment of acute psychoses, the dose of antipsychotic drug is increased during the first few days to achieve control of symptoms. The dose is then adjusted during the next several weeks as the patient's condition warrants. Parenteral medication sometimes is indicated for acutely agitated patients; 5 mg of haloperidol or fluphenazine or comparable doses of another agent are given intramuscularly. The desired response usually can be obtained by administering additional doses at intervals of 4 to 8 hours for the first 24 to 72 hours because the appearance of effects may be delayed for several hours. Rarely is it necessary to administer more than 20 to 30 mg of fluphenazine or haloperidol (or an equivalent amount of another agent) per 24 hours. Severe and otherwise poorly controlled agitation usually can be managed safely by use of adjunctive sedation (*e.g.*, with a benzodiazepine such as lorazepam) and close supervision in a secure setting. One must remain alert for acute dystonic reactions, which are especially likely early in the aggressive use of potent neuroleptics. Hypotension is most likely to occur if an agent of low potency, such as chlorpromazine, is given in a high dose or by injection. Some antipsychotic drugs, including fluphenazine, other piperazines, and haloperidol, have been given in doses of several hundred milligrams a day without disaster, although such high doses of potent agents do not yield significantly or consistently superior results in the treatment of acute or chronic psychosis, and they may yield inferior antipsychotic effects as well as be associated with

increased risks
Lader, 1980; B
bilization, regin
per day of halo
tive and safe; th
which unwante
comfort.

Table 18–
antipsychotic d
established, f
manic patient
higher doses
tients, the co
fice during f
chotic patient
(Baldessarini

In reviews
close to 3,500
was 58% for th
drugs and give
continued on c
1996b). Dosag
of chlorproma.
lapse. Flexible
rent requireme
effects. Maint.
fluphenazine o
(Kane *et al.*, 1

The treat
is another acce
ministered ten
infectious, me
sometimes use
be found. Onc
lished dosage
potency are pr
"syndromes" w
2 to 6 mg) of
trolling agitati
cause of their
seizures, and
confusion and
likely than se
pairment in d

The use
with some su
of mania and
lithium therap
carbamazepin
tempt to man
week of illne
sedative dose
the treatment
preventive eff
have been co
the treatment
the efficacy o
especially th
addition of a
may yield res
al., 1987; Ch

increased risks of neurological and other side effects (Aubree and Lader, 1980; Baldessarini *et al.*, 1988). After an initial period of stabilization, regimens based on a single daily dose (typically 5 to 10 mg per day of haloperidol, fluphenazine, or their equivalent) are effective and safe; this may allow some degree of selection of the time at which unwanted effects occur so as to minimize the patient's discomfort.

Table 18–1 gives the usual and extreme ranges of dosage for antipsychotic drugs used in the United States. The ranges have been established, for the most part, in the treatment of schizophrenic or manic patients. Although acutely disturbed inpatients often require higher doses of an antipsychotic drug than do more stable outpatients, the concept that a low or flexible maintenance dose will suffice during follow-up care of a partially recovered or chronic psychotic patient is supported by several appropriately controlled trials (Baldessarini *et al.*, 1988; Herz *et al.*, 1991; Kane *et al.*, 1983).

In reviews of nearly 30 controlled prospective studies involving close to 3,500 schizophrenic patients, the mean overall relapse rate was 58% for those patients who were withdrawn from antipsychotic drugs and given a placebo, compared with only 16% of those who continued on drug therapy (Baldessarini *et al.*, 1990; Baldessarini, 1996b). Dosage in chronic cases often can be lowered to 50 to 200 mg of chlorpromazine (or its equivalent) per day without signs of relapse. Flexible therapy in which dosage is adjusted to changing current requirements can be useful and can reduce the incidence of side effects. Maintenance with injections of the decanoate ester of fluphenazine or haloperidol every 2 to 4 weeks can be very effective (Kane *et al.*, 1983).

The treatment of cognitive disorders (*i.e.*, delirium or dementia) is another accepted use of the antipsychotic drugs. They may be administered temporarily, while a specific and correctable structural, infectious, metabolic, or toxic cause is vigorously sought. They are sometimes used for prolonged periods when no correctable cause can be found. Once again, there are no drugs of choice or clearly established dosage guidelines for such indications, although agents of high potency are preferred (*see* Prien, 1973). In patients with acute "brain syndromes" without likelihood of seizures, frequent small doses (*e.g.*, 2 to 6 mg) of haloperidol or a piperazine may be effective in controlling agitation. Agents with low potency should be avoided because of their greater tendency to produce sedation, hypotension, and seizures, and those with central anticholinergic effects may worsen confusion and agitation. The potent antipsychotic drugs are much less likely than sedatives to cause additional confusion or memory impairment in delirious or demented patients.

The use of antipsychotic drugs in mania and depression has met with some success. Most neuroleptics are effective in the treatment of mania and often are used concomitantly with the institution of lithium therapy or anticonvulsant agents such as sodium valproate or carbamazepine (*see* Chapter 19). In fact, it often is impractical to attempt to manage a manic patient with lithium alone during the first week of illness, when the antipsychotic drugs usually are required; sedative doses of potent anxiolytic agents also can be used early in the treatment of mania. No adequate studies of possible long-term preventive effects of antipsychotic drugs in manic-depressive illness have been conducted. Neuroleptics also may have a limited role in the treatment of depression. Controlled studies have demonstrated the efficacy of several antipsychotic drugs in some depressed patients, especially those with striking agitation or psychotic delusions, and addition of a neuroleptic to an antidepressant in psychotic depression may yield results approaching those obtained with ECT (Brotman *et al.*, 1987; Chan *et al.*, 1987).

Anxiety has been considered a possible indication for the use of antipsychotic drugs, especially in small doses. In view of the wide range of disturbing and serious side effects, the routine use of these drugs for such a purpose is inappropriate. In rare instances, patients who have crippling anxiety that does not respond to sedative-antianxiety drugs or to treatment with antidepressant agents may benefit from a brief trial of an antipsychotic agent. A brief trial is not likely, however, to be of long-term benefit to a patient who suffers from debilitating anxiety. Long-term treatment may involve risks such as the development of tardive dyskinesias that far outweigh the uncertain benefits of using neuroleptics to relieve symptoms of anxiety.

The status of the drug treatment of childhood psychosis and other behavioral disorders of children is confused by diagnostic inconsistencies and a paucity of controlled studies. Neuroleptics can benefit children with disorders characterized by features that occur in adult psychoses, as well as those with Tourette's syndrome. Low doses of the more potent agents usually are preferred in an attempt to avoid interference with daytime activities or performance in school (Biederman and Jellinek, 1984). Attention disorder, with or without hyperactivity (attention deficit hyperactivity disorder), responds poorly to antipsychotic agents but often very well to certain stimulants. Methylphenidate is commonly used, but amphetamines also are effective, and sometimes pemoline is employed. For patients who respond poorly or inconsistently to stimulants or develop adverse effects such as weight loss, dysphoria, or tics, antidepressant agents sometimes are employed. The tricyclic type of antidepressants have been characterized in the most detail, but serotonin reuptake inhibitors also may be effective in some cases (*see* Chapter 19; Biederman *et al.*, 1989; Zametkin and Rapoport, 1987). Information on dosages of antipsychotic drugs for children is limited, as is the number of drugs currently approved in the United States for use in preadolescents. The recommended doses of antipsychotic agents for school-aged children with moderate degrees of agitation are lower than those for acutely psychotic children, who may require doses similar to those used in adults (total milligrams per day) (Baldessarini, 1996a; Biederman and Jellinek, 1984; Popper, 1987; *see* also Table 18–1). Most relevant experience is with chlorpromazine, for which the recommended single dose is approximately 0.5 mg/kg of body weight, given at intervals of 4 to 6 hours orally or 6 to 8 hours intramuscularly. Suggested dosage limits are 200 mg per day (orally) for preadolescents, 75 mg per day (intramuscularly) for children age 5 to 12 years or weighing 23 to 45 kg, and 40 mg per day (intramuscularly) for children under 5 years of age or 23 kg of body weight. Usual single doses for other agents of relatively low potency are triflupromazine, 0.25 mg/kg; thioridazine, 0.25 to 0.5 mg/kg; and chlorprothixene, 0.5 to 1.0 mg/kg, to a total of 100 mg/day (over the age of 6). For neuroleptics of high potency, daily doses are trifluoperazine, 1 to 15 mg (6 to 12 years of age) and 1 to 30 mg (over 12 years of age); fluphenazine, 0.05 to 0.10 mg/kg, up to 10 mg (over 5 years of age); and perphenazine, 0.05 to 0.10 mg/kg, up to 6 mg (over 1 year of age). Haloperidol and pimozide have been used in children, especially for Tourette's syndrome; haloperidol is recommended for use in a dosage of 2 to 16 mg per day in children over 12 years of age.

Poor tolerance of the side effects of the antipsychotic drugs often limits the dosage that can be given to elderly patients. One should proceed cautiously, using small, divided doses of agents with moderate or high potency, with the expectation that elderly patients will require doses that are one-half or less of those needed for young adults (*see* Jenike, 1985; Raskin *et al.*, 1981).

MISCELLANEOUS MEDICAL USES FOR NEUROLEPTIC DRUGS

Neuroleptic drugs have a variety of uses in addition to the treatment of psychiatric patients. Predominant among these are the treatment of nausea and vomiting, alcoholic hallucinosis, certain neuropsychiatric diseases marked by movement disorders (notably, Tourette's syndrome and Huntington's disease), and, occasionally, pruritus (for which trimeprazine is recommended) and intractable hiccough.

Nausea and Vomiting. Many antipsychotic agents can prevent vomiting of specific etiologies when given in relatively low, nonsedative doses. This use is discussed in Chapter 38.

Other Neuropsychiatric Disorders. Antipsychotic drugs are useful in the management of several syndromes with psychiatric features that are also characterized by movement disorders. These include, in particular, *Tourette's syndrome* (marked by tics, other involuntary movements, aggressive outbursts, grunts, and vocalizations that frequently are obscene; *see* Shapiro *et al.*, 1988) and *Huntington's disease* (marked by severe and progressive choreoathetosis, psychiatric symptoms, and dementia, with a clear genetic basis; *see* Chase, 1976). Haloperidol is currently regarded as the drug of choice for these conditions, although it is probably not unique in its antidyskinetic actions. Pimozide, a diphenylbutylpiperidine, also is used (typically in daily doses of 2 to 10 mg). Pimozide carries some risk of impairing cardiac repolarization, and it should be discontinued if the Q-T interval exceeds 470 msec, especially in a child. Clonidine and certain antidepessants also may be effective in Tourette's syndrome (Spencer *et al.*, 1993).

Withdrawal Syndromes. Antipsychotic drugs are *not* useful in the management of withdrawal from opioids, and their use in the management of withdrawal from barbiturates and other sedatives or alcohol is contraindicated, because of the high risk of seizures. They can be used safely and effectively in psychoses associated with chronic alcoholism—especially the syndrome known as *alcoholic hallucinosis* (*see* Kaplan and Sadock, 1989).

II. DRUGS USED IN THE TREATMENT OF ANXIETY

Anxiety is a cardinal symptom of many psychiatric disorders and an almost-inevitable component of many medical and surgical conditions. Indeed, it is a universal human emotion, closely allied with appropriate fear, and often serving psychobiologically adaptive purposes. A most important clinical generalization is that anxiety is rather infrequently a "disease" in itself. Anxiety that is typically associated with the "psychoneurotic" disorders is not readily explained in biological or psychological terms; contemporary hypotheses implicate overactivity of adrenergic systems or dysregulation of serotonergic systems in the CNS (Hoehn-Saric, 1982; Gorman *et al.*, 1987; Coplan *et al.*, 1992). In addition, symptoms of anxiety commonly are associated with depression and especially with dysthymic disorder (chronic "neurotic" depression), panic disorder, agoraphobia and other specific phobias, obsessive-compulsive disorder, eating disorders, and many personality disorders. Sometimes, despite a thoughtful evaluation of a patient, no treatable primary illness is found, or, if one is found and treated, it may be desirable to deal directly with the anxiety at the same time. In such situations, antianxiety medications are frequently and appropriately used (*see* Hollister *et al.*, 1993; Janicak *et al.*, 1993; Lader, 1994).

Currently, the benzodiazepines are the most commonly employed antianxiety agents for generalized anxiety disorder. Some benzodiazepines (alprazolam, clonazepam, and lorazepam) are effective in severe anxiety with strong autonomic overactivity (panic disorder) as are several antidepressant agents (*see* Chapter 19; Dubovsky, 1990; Lader, 1994; Rickels and Schweizer, 1987; Symposium, 1982, 1983, 1988). For generalized or nonspecific anxiety, the specific agent selected seems to make little difference. In the elderly or in patients with impaired hepatic function, oxazepam in small, divided doses is currently favored due to its brief action and direct conjugation and elimination. The latter property is shared by lorazepam, but not by alprazolam, which requires ring-oxidation before conjugation, although its elimination half-life is slightly shorter than that of lorazepam (12 vs. 14 hours; *see* Chapter 17). Benzodiazepines commonly are given to outpatients with anxiety mixed with symptoms of depression, although their specific efficacy in the core features of severe major depression is not well demonstrated. Potent benzodiazepines also are commonly employed, adjunctively, in the short-term management of acutely psychotic or manic patients (*see* Chapter 19; Baldessarini, 1996a).

The most favorable responses to the benzodiazepines are obtained in situations that involve relatively acute anxiety reactions in medical or psychiatric patients who have either modifiable primary illnesses or primary anxiety disorders. However, this group of anxious patients also has a high response rate to placebo and is likely to undergo spontaneous improvement. Antianxiety drugs also are used in the management of more persistent or recurrent anxiety associated with the neuroses; guidelines for their appropriate use are less clear in these situations. Although there has been concern about the potential for habituation and abuse of sedatives, some studies suggest that physicians tend to be conservative and may even undertreat patients with anxiety. They may either withhold drug unless symptoms or dysfunction are severe or cease treatment within a few weeks, with a high proportion of relapses. Patients with personality disorder or a past history of abuse of sedatives or alcohol may be particularly at risk of dose-escalation and dependence on benzodiazepines. Benzodiazepines carry some risk of producing impairment of cognition and skilled motor functions, particularly in the elderly, in whom they are

a common cause of confusion, delirium (sometimes mistaken for primary dementia), and falls with fractures (Ray *et al.*, 1987); azapirones are less likely to produce these impairments. Risk of fatality on acute overdose of benzodiazepines is limited in the absence of other cerebrotoxins or alcohol; risk of suicide with buspirone is very low. A particularly controversial aspect of the use of benzodiazepines, especially those of high potency, is in long-term management of patients with sustained or recurring symptoms of anxiety. Benefits have been found for at least several months in such cases, but it is unclear to what extent the long-term benefits can be distinguished from nonspecific ("placebo") effects following development of tolerance, on the one hand, or prevention of related withdrawal-emergent anxiety on the other (Lader, 1994). The status of sedative-antianxiety agents as federally controlled substances is reviewed in Appendix I.

Sedatives with useful antianxiety effects are consistently among the most commonly prescribed drugs. The appropriate generic term for this group of agents remains uncertain, and terms such as *antianxiety agents, anxiolytics,* and *tranquilizers* are currently used. Most drugs used to treat anxiety are sedatives or at least have many properties in common with traditional sedatives, such as the barbiturates. Even the benzodiazepines have sedative properties, particularly when relatively high doses are given. The wide diversity of compounds used to treat anxiety greatly complicates attempts to make generalizations about them. Many of these drugs are discussed in other chapters of this text (*see* Chapters 17, 20, and 24). This section covers a limited group of agents that are commonly used to treat anxiety and mild dysphoria, and only this use is emphasized. Because the benzodiazepines dominate this field, they are given the most attention. Several reviews of the pharmacology of these drugs, particularly the benzodiazepines, are available (*see* Hollister *et al.,* 1993; Neumeyer and Booth, 1995; Rosenbaum, 1987; Symposium, 1988; *see also* Chapter 17).

History. Human beings have sought chemical agents to modify the effects of stress and the feelings of discomfort, tension, anxiety, and dysphoria throughout recorded history. Many of these efforts have led to the development of agents that are often classed as sedatives, and the single most widely used of these is one of the oldest—ethanol. In the past century, bromide salts and compounds similar in effect to alcohol, including paraldehyde and chloral hydrate, were introduced into medical practice as sedatives; these were followed in the early 1900s by the barbiturates. The barbiturates were the dominant antianxiety agents throughout the first half of this century; however, by the 1950s concern had arisen about their propensity to induce tolerance, physical dependence, and potentially lethal reactions during withdrawal, and this encouraged the search for safer agents. Compounds such as meprobamate were the initial result. Despite the initial popularity of some of these compounds for daytime sedation or for hypnotic effects, they share many of the undesirable properties of barbiturates, including a limited degree of separation between their useful antianxiety effects and excessive sedation as well as a propensity to cause physical dependence and severe acute intoxication on overdosage (Greenblatt and Shader, 1971). This set the scene for the discovery of chlordiazepoxide in the late 1950s and the synthesis of over 3000 benzodiazepines, nearly 50 of which are clinically employed. This class of sedatives has come to dominate the market and medical practice; in recent years, alprazolam, diazepam, lorazepam, and their congeners have been among the front-runners in terms of numbers of prescriptions written for all drugs used in medical practice.

BENZODIAZEPINES

Nine benzodiazepine derivatives currently are recommended for the treatment of anxiety. In their order of introduction, they are *chlordiazepoxide, diazepam, oxazepam, clorazepate, lorazepam, prazepam, alprazolam,* and *halazepam;* in addition, *clonazepam* (noted more for its potent anticonvulsant properties) is used in the treatment of panic disorder (*see* Rosenbaum, 1987). Although commonly used for treating anxiety, these drugs share other therapeutic indications—notably sedation and induction of sleep. While other benzodiazepines are advertised with an emphasis on sedative or hypnotic effects, the differences between them and the nine recommended for anxiety are subtle and possibly insignificant (*see* Greenblatt *et al.,* 1983). The available preparations and dosages recommended for the use of benzodiazepines for treatment of anxiety are provided in Table 18–3.

History. The first successful benzodiazepine, *chlordiazepoxide,* was developed by Sternbach's group at the Roche Laboratories in the late 1950s (Neumeyer and Booth, 1995). Chlordiazepoxide had muscle-relaxant and spinal reflex-blocking properties in animals. It also produced "taming" in animals at doses much lower than those producing ataxia or inducing sleep. These findings led to the clinical trial of the drug in human beings for the determination of antianxiety effects (*see* Symposium, 1982.)

Chemistry. The structure–activity relationships of the benzodiazepines have been reviewed by Sternbach (*see* Symposium, 1982). Structures of benzodiazepines commonly recommended for treatment of anxiety are shown in Chapter 17 (Figure 17–1; *see also* Neumeyer and Booth, 1995).

Chlordiazepoxide, diazepam, and lorazepam can be considered prototypical drugs of their class.

Central Nervous System. ***Behavioral and Neurophysiological Effects.*** The effects of the benzodiazepines in the relief of anxiety can be demonstrated readily in experimental animals (Eison, 1984). In conflict punishment procedures, benzodiazepines greatly reduce the suppressive

Compounds Used for Anxiety: Dosage Forms and Doses

NONPROPRIETARY NAME	TRADE NAME	DOSAGE FORMS *	USUAL DAILY DOSE, *mg* †	EXTREME DAILY DOSE, *mg*
Alprazolam	XANAX	O	0.75–1.5	0.5–4
Chlordiazepoxide	LIBRIUM, others	O, I	15–40 25–200 (parenteral; may repeat in 2–4 hr)	10–100 25–300 (parenteral)
Clonazepam ‡	KLONOPIN	O	1.5–10	0.5–20
Clorazepate	TRANXENE	O §	15–60	7.5–90
Diazepam	VALIUM, others	O §, I, L	4–40 2–20 (parenteral; may repeat in 3–4 hr)	2–40
Halazepam	PAXIPAM	O	60–160	20–160
Lorazepam	ATIVAN, others	O, I	2–6 2–4 (parenteral)	1–10
Oxazepam	SERAX, ZAXOPAM	O	30–60	30–120
Prazepam	CENTRAX	O	20–40	10–60
Buspirone	BUSPAR	O	20–30	15–60

* Dosage forms: O, oral solid; I, injection; L, oral liquid.

† The daily doses are given as total milligrams per day, assuming doses are divided into two or four portions per day. Single parenteral doses are giv[en] for chlordiazepoxide and diazepam. All doses are for adults or adolescents. For children 6 to 12 years of age, chlordiazepoxide may be giv[en] orally in divided daily doses of 10 to 30 mg. Diazepam may be given in divided daily doses of 3 to 10 mg to children over 6 months of age. F[or] younger children, consult the manufacturer's instructions. Clorazepate is not recommended for children less than 9 years of age.

‡ Clonazepam is used primarily as an anticonvulsant, but has been used in panic disorder, as an adjunctive treatment of acute mania, and to facilit[ate] withdrawal from other benzodiazepines that have a shorter duration of action.

§ Clorazepate also is available as slow-release tablets (TRANXENE-SD) to be taken once daily. Diazepam also is available in slow-release capsules (VA[LRELEASE]).

effects of punishment. Positive effects in this experimental model are not seen with antidepressants and antipsychotics.

Difficulties in evaluating the therapeutic efficacy of psychotropic drugs in human beings are particularly great in the case of the antianxiety drugs, because of the contribution of nonpharmacological factors to the treatment of anxiety; disparate results have thus been obtained. Many studies have shown that benzodiazepines are more effective than a placebo in the treatment of varied groups of anxious neurotic patients. However, negative results also have been reported (*see* Janicak *et al.*, 1993). The clinical popularity of these drugs apparently is the result of a combination of their pharmacological actions, their relative safety, and an extraordinary demand for agents of this type by both physicians and patients.

In common with barbiturates, chlordiazepoxide blocks EEG arousal from stimulation of the brainstem reticular formation. Benzodiazepines exert central-depressant actions on spinal reflexes, in part mediated by the brainstem reticular system. Like meprobamate and the barbiturates, chlordiazepoxide depresses the duration of electrical afterdischarge in the limbic system, including the septal region, the amygdala, the hippocampus, and the hypothalamus. Virtually all benzodiazepines elevate seizure threshold and are anticonvulsant. Clonazepam, diazepam, and clorazepate are used clinically for this purpose (*see* Chapter 20).

There is also much interest in the effects of benzodiazepines on neurotransmission in the forebrain that is mediated by gamma-aminobutyric acid (GABA). One of the most important inhibitory neurotransmission systems in the brain is mediated by $GABA_A$ receptors and Cl^- ion channels (*see* Chapters 12 and 17). Research on this system has been stimulated by electrophysiological observations of the potentiation of the inhibitory effects of GABA by benzo-

diazepines (as well as by alcohol and barbiturates) and by the discovery of specific binding sites for benzodiazepines in various brain regions, particularly cerebellum, cerebral cortex, and the limbic system (Potokar and Nutt, 1994). These sites are believed to occur in a protein macromolecular complex that includes the large family of $GABA_A$ receptors and a Cl^- channel (Burt and Kamatchi, 1991). Binding of benzodiazepines can be modulated by both GABA and Cl^- even after extensive purification of the binding sites. Several imidazole–benzodiazepines, which act as benzodiazepine antagonists (*e.g.*, flumazenil or Ro 15-1788), and carboline compounds with opposite physiological actions to those of benzodiazepines [inverse agonists, including ethyl-β-carboline-3-carboxylate (β-CCE) and its 6,7-dimethoxy congener (DMCM)] competitively inhibit the binding of the benzodiazepines. At concentrations in the therapeutic range, benzodiazepines also can reduce the excitability of some neurons by actions that involve neither GABA nor alterations in membrane permeability to Cl^-. Thus, cellular mechanisms in addition to the important facilitation of GABA-mediated Cl^- conductance may contribute to the behavioral effects of benzodiazepines. (*see* Burt and Kamatchi, 1991; Polc, 1988; Symposium, 1988; *see also* Chapter 17.)

Effects on Sleep. Benzodiazepines can be used effectively as hypnotics in conjunction with their use as antianxiety drugs (Chapter 17). They seem to have only mild capacity to suppress REM sleep, but they do have a tendency to suppress the deeper phases of sleep, especially stage 4 (while *increasing* total sleep time). The significance of this finding is not known, but diazepam has been used in the treatment of "night terrors" that arise in stage-4 sleep.

Cardiovascular and Respiratory Systems. The cardiovascular effects of the benzodiazepines are mild, and this encourages their frequent use in cardiac patients. Diazepam, in an intravenous dose of 5 to 10 mg, causes a slight decrease in respiration, blood pressure, and left ventricular stroke work. Increase in heart rate and decrease in cardiac output also can occur. The effects are minimal, and it is unlikely that benzodiazepines given in usual therapeutic doses by the oral route significantly depress cardiovascular function.

Skeletal Muscle. Diazepam and other benzodiazepines are widely used as muscle relaxants, although controlled studies have been inconsistent in showing an advantage of benzodiazepines over either placebo or aspirin. Some muscle relaxation occurs after administration of most CNS depressants, and the advantages of the benzodiazepines appear to be small when given orally (*see* Chapter 17).

Absorption, Distribution, Fate, and Excretion. Prazepam, clonazepam, and oxazepam are absorbed relatively slowly following oral administration, and peak concentrations in plasma may not be attained for hours. In contrast, diazepam is absorbed rapidly, reaching peak concentrations in about an hour in adults, and as quickly as 15 to 30 minutes in children. Alprazolam, chlordiazepoxide, halazepam, and lorazepam have intermediate rates of absorption. Clorazepate and prazepam do not appear as such in the blood. Clorazepate is quickly decarboxylated in the gastrointestinal tract, and the product, N-desmethyldiazepam (*nordazepam; desoxydesmoxepam*), is rapidly absorbed; prazepam is absorbed slowly and is transformed primarily to nordazepam by the liver before reaching the systemic circulation. Several other benzodiazepines also are converted to nordazepam *in vivo,* including chlordiazepoxide, diazepam, and halazepam (*see* Greenblatt *et al.*, 1981). With the exception of lorazepam, the benzodiazepines are unpredictably absorbed following intramuscular injection but are rapidly absorbed when administered sublingually (*see* Greenblatt *et al.*, 1983).

Most of the benzodiazepines are bound to plasma protein to a great extent (85% to 95%)—a factor that limits the efficacy of dialysis in the treatment of acute poisoning. The apparent volumes of distribution for most benzodiazepines range from 1 to 3 liters per kilogram.

The pharmacokinetic parameters that have been reported for these agents often can be misleading, because active metabolites with long half-lives can markedly alter the duration of effects. Notably, the formation of long-acting nordazepam as an active metabolite of several benzodiazepines can extend the duration of their effects severalfold. A striking example is halazepam (half-life in plasma of 14 hours), the duration of action of which largely reflects its metabolic conversion to nordazepam, which has a half-life of up to 100 hours. Nordazepam subsequently is 3-hydroxylated to another active compound, oxazepam, before inactivation by conjugation with glucuronic acid. Halazepam is no longer available for use in the United States. The metabolism of the benzodiazepines is described further in Chapter 17 and summarized in Table 17–1.

The half-life usually stated for the elimination phase of the more lipophilic benzodiazepines does not adequately depict the kinetics of the early distributive phase, which can be important clinically. For example, the distributive (alpha) half-life of diazepam is about 1 hour, while the elimination (beta) half-life is about 1.5 days initially and even longer after prolonged treatment. Diazepam is rapidly absorbed and delivered to highly perfused tissues, including the brain, where a rapid psychotropic effect is produced. The drug is then redistributed to less well perfused tissues. Thus, diazepam has a rapid onset and a relatively brief duration of action after a single dose due to redistribution out of the brain, even though the elimination half-life is long. Moreover, while correlations between plasma concentrations of benzodiazepines and clinical effects are

limited, concentrations in plasma only twice those usually considered to be effective are associated with undesirable degrees of sedation. For this reason, benzodiazepines are neither effectively nor safely given once a day; even those with relatively long elimination half-lives are best given in two to four portions for the treatment of daytime anxiety to avoid early intoxication and later reemergence of anxiety symptoms or mild withdrawal.

The benzodiazepines as a class tend to have minimal pharmacokinetic interactions with other drugs, although their oxidative metabolism may be inhibited by cimetidine, disulfiram, isoniazid, and oral contraceptives and appears to be increased by rifampin. The premature neonate and the elderly may have half-lives for diazepam that are three or four times longer than those of young adults, children, or even full-term neonates. In addition, severe hepatic disease can increase the half-life of diazepam by a factor of two to five. Since formation of glucuronides is not restricted to hepatic endoplasmic reticulum, oxazepam and lorazepam may be safer for patients with severely impaired hepatic function, if they are given in small divided doses. Oxazepam may be safer for elderly patients because of its relatively short duration of action. Most of the benzodiazepines are excreted almost entirely in the urine and in the form of oxidized and glucuronide-conjugated metabolites (*see* Chapter 17).

Information on the pharmacokinetic properties and metabolism of the benzodiazepines is described by Greenblatt *et al.* (1981). (*See* also Symposium, 1982, and Appendix II.)

Tolerance and Physical Dependence. If doses of benzodiazepines are given for long periods of time and then abruptly withdrawn, severe withdrawal symptoms, which occasionally include seizures, can occur (Woods *et al.*, 1987). Because of the long half-lives and conversion to active metabolites with long durations of action, withdrawal or abstinence symptoms after prolonged use may not appear for a week or more after abrupt discontinuation of the drug and are likely to be mild (Lader, 1994; Rickels *et al.*, 1988; Woods *et al.*, 1987). In most instances after gradual withdrawal of usual doses of long-acting agents, no abstinence syndrome occurs. However, some observations suggest that potent benzodiazepines with relatively short durations of action may be associated with the emergence of symptoms of anxiety between doses; difficulty in discontinuing treatment also has been noted. It is not clear to what extent these phenomena represent dependence or mild withdrawal reactions, in contrast to the reemergence of primary symptoms for which the treatment was originally given. Alprazolam and lorazepam appear to be associated most often with such reactions. Substitution of a longer-acting benzodiazepine (*e.g.*, 1 mg of clonazepam for each 1 to 2 mg of alprazolam or lorazepam) may provide more sustained anxiolytic effects and facilitate gradual withdrawal (Rosenbaum, 1987).

Toxic Reactions and Side Effects. The expected side effects of CNS depressants of drowsiness and ataxia are extensions of the pharmacological actions of these drugs.

With diazepam, antianxiety effects can be expected at blood concentrations of 300 to 400 ng/ml, while some sedative effects and psychomotor impairment begin at similar concentrations; gross CNS intoxication can be expected at concentrations over 900 to 1000 ng/ml (Morselli, 1977). Therapeutic concentrations of chlordiazepoxide are approximately 700 to 1000 ng/ml.

An increase in hostility and irritability, and vivid or disturbing dreams, are sometimes associated with the benzodiazepines. In addition, one of the most common causes of reversible confusional states in the elderly is the overuse of sedatives of all kinds, including what would ordinarily be referred to as "small" doses of benzodiazepines.

Weight gain, which may be the result of renewed appetite, occurs in some patients. Among the other toxic reactions seen with chlordiazepoxide are skin rash, nausea, headache, impairment of sexual function, vertigo, and lightheadedness. Agranulocytosis and hepatic reactions rarely have been reported. Menstrual irregularities have been noted, and women may fail to ovulate while taking benzodiazepines.

Overdosage with the benzodiazepines is frequent, but serious sequelae are rare unless other drugs or ethanol are also taken. A few deaths have been reported at doses greater than 700 mg of diazepam or chlordiazepoxide. The striking advantage of this group of drugs is their remarkable margin of safety. Treatment for overdosage is purely supportive of respiratory and cardiovascular function. The discovery that certain imidazobenzodiazepines (notably, flumenazil) have selective, antagonistic effects against the benzodiazepines might yield the development of clinically useful antidotes for patients who have overdosed (Brogden and Goa, 1988; *see also* Chapter 17).

The question of teratogenic effects of benzodiazepines or other toxic effects on the fetus is controversial (Cziezel and Lendvay, 1987; Laegreid *et al.*, 1992). The most persistent, but still unproven, suggestion has been that there may be a small increase in the risk of midline cleft deformities of the lip or palate, although these remain well below the overall risk of birth defects (about 2% to 5% in the general population) and are correctable by surgery. Benzodiazepines depress CNS function in the neonate, and especially in the premature newborn. Concentrations of these drugs in umbilical cord blood may exceed those in the maternal circulation; as mentioned, the fetus and newborn are much less able to metabolize benzodiazepines than are adults. Thus, intrauterine exposure to benzodiazepines potentially can lead to a need for respiratory support after delivery.

Interactions with Other Drugs. Interactions with other drugs are infrequent with the benzodiazepines, and, except for an additive effect with other CNS depressants, they are usually not significant. Minor pharmacokinetic interactions are mentioned above. Heavy cigarette smoking may decrease the effectiveness of usual doses of these drugs.

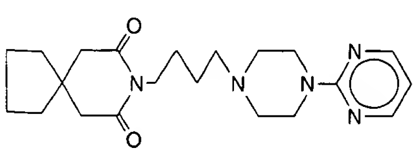
OTHER SEDATIVES USED FOR ANXIETY

Many other classes of drugs that act on the CNS have been used for daytime sedation and the treatment of anxiety, but their use for these conditions is now virtually obsolete. Such drugs include the *propanediol carbamates* (notably, *meprobamate* and *tybamate*), the barbiturates (*see* Chapter 17), and many other pharmacologically similar nonbarbiturates.

The demise of older sedative agents in modern psychiatric practice is due primarily to their tendency to cause unwanted degrees of sedation or frank intoxication at doses required to alleviate anxiety; meprobamate and the barbiturates are likely to produce tolerance, physical dependence, severe withdrawal reactions, and life-threatening toxicity with overdosage.

Other drugs that have been used in the treatment of anxiety include certain anticholinergic agents and antihistamines. Among these is *hydroxyzine*, an antihistamine that is not an effective antianxiety agent unless given in doses (400 mg per day) that produce marked sedation (Goldberg, 1984; *see also* Chapter 25). *Propranolol* and other β-adrenergic receptor antagonists can reduce the autonomic symptoms associated with specific situational phobias, but do not appear to be effective in generalized anxiety or panic disorder; similarly, other anti-adrenergic agents including clonidine may modify autonomic expression of anxiety, but have not been demonstrated convincingly to be clinically useful in the treatment of severe anxiety disorders (Rickels and Schweizer, 1987; Tyrer, 1980).

A recently introduced new class of agents with beneficial effects in disorders marked by anxiety or dysphoria of moderate intensity are the *azapirones* (azaspirodecanediones), currently represented clinically by *buspirone* (Table 18–3).



BUSPIRONE

Originally developed as a potential antipsychotic agent with weak antidopaminergic activity, buspirone has pharmacological properties distinct from those of both neuroleptics and sedatives including the benzodiazepines (Rickels *et al.*, 1988; Sussman, 1994; Yocca, 1990). Their antidopaminergic actions are limited *in vivo*, and they do not induce clinical extrapyramidal side effects. Also, they do not interact with binding sites for benzodiazepines or facilitate the action of GABA, are not anticonvulsant (and may even lower seizure threshold weakly), do not appear to cause tolerance or withdrawal reactions, and do not show cross-tolerance with benzodiazepines or other sedatives. Buspirone and several experimental congeners (*e.g.*, gepirone, ipsapirone, tiaspirone) have selective affinity for serotonin receptors of the 5-HT_{1A} type, for which they appear to be partial agonists (*see* Chapter 11).

Azapirones have selective affinity at serotonin 5-HT_{1A} receptors labeled with the radioligand 8-hydroxy-2-(dipropylamino) tetralin (8-OH-DPAT) and low affinity for 5-HT_2 receptors. They are relatively active agonists of somatodendritic 5-HT_{1A} autoreceptors, while showing variable postsynaptic 5-HT_{1A} antagonism. Agonist effects of azapirones at presynaptic 5-HT_{1A} autoreceptors include decreased firing of dorsal raphe serotonin neurons and decreased synthesis and release of serotonin. These are blocked selectively by 5-HT_{1A} antagonists such as (−)-pindolol. Long-term antiserotonergic actions of azapirones may lead to adaptations, including decreases of 5-HT_2 (but probably not 5-HT_{1A}) receptors in cerebral cortex.

Azapirones also have moderate interactions with cerebral dopaminergic and noradrenergic systems, with a tendency to increase turnover of both catecholamines, possibly through action at autoreceptors. They fail to induce catalepsy and can reverse cataleptic effects of neuroleptics, but antagonize some actions of full dopamine agonists while appearing to act as agonists at deafferented dopamine receptors. At high doses, they also have weak prolactin-elevating actions in animals that are not found at moderate clinical doses. The azapirones fail to compete with benzodiazepine binding sites or facilitate the action of GABA but may, instead, have some antagonist interactions with GABAergic transmission (with no evidence of inducing seizures).

A major metabolite of buspirone and its dimethyl congener *gepirone* is 1-(2-pyrimidyl)-piperazine (1-PP), formed by dealkylation of the butyl side chain at a piperazine nitrogen. This by-product is found in brain tissue at much higher concentrations than the parent compounds. It has some pharmacological activity, including antagonism of α_2-adrenergic receptors, but probably little action at serotonergic sites, and limited antianxiety effect. It is further oxidized to 5-hydroxy-1-PP, the major urinary metabolite, although hydroxylation may precede dealkylation. Buspirone is poorly bioavailable (5% or less), is largely protein-bound in plasma (95%) with an apparent volume of distribution of 5 liters/kg, and has an elimination half-life of about 2.5 hours.

Buspirone has beneficial actions in anxious patients, particularly those with generalized anxiety of limited severity (Taylor, 1988). Unlike potent benzodiazepines and certain antidepressant drugs (*see* Chapter 19), buspirone lacks beneficial actions in severe anxiety with panic attacks. It also does not share with antidepressants their efficacy as a monotherapy in obsessive-compulsive disorder and attention deficit hyperactivity disorder, although some reports suggest useful antiobsessional activity when buspirone is added to serotonin-active antidepressants. A lack of cross-tolerance is consistent with a lack of clinical protection against withdrawal-emergent anxiety when changing abruptly from treatment with a benzodiazepine to buspirone; a gradual transition between these classes of antianxiety agents is more likely to be tolerated (Lader and Olajide, 1987). The central adrenergic facilitating actions of buspirone may worsen withdrawal responses to benzodiazepines. On the other hand, such effects may contribute

to clinical observations of moderate mood-elevating or antidysphoric actions of buspirone. Complete understanding of the actions and optimal clinical application of the azapirones requires further research.

Broader recent acceptance of clozapine for general use has stimulated an unprecedented interest in antipsychotic agents with a low risk of extrapyramidal neurological side effects and high efficacy. Clozapine may have both of these desirable properties (Baldessarini and Frankenburg, 1991; Zarate *et al.*, 1995). However, the risks of seizures (at high doses), sedation, weight-gain, fever, leukopenia, and potentially lethal agranulocytosis associated with clozapine complicate its use, limit its broad acceptance, and have led to a search for safer alternatives. Several benzepine analogs are known and have had some clinical assessment. These include *fluperlapine* (withheld due to leukopenia), *olanzapine* (an analogous thienobenzodiazepine), *zotapine,* and *seroquel* (ICI-204,636), which remain in clinical trials (Meltzer, 1992; Moore *et al.*, 1992). Most of these agents have a complex neuropharmacology, resembling that of clozapine, with interactions at several classes of receptors.

A related approach stimulated by clozapine is to test agents with antidopaminergic plus other actions, particularly antagonism of central 5-HT_2 serotonin receptors. The benzepine compounds mentioned above have these properties, as does the benzisoxazole risperidone. Its superiority to other neuroleptics has not been proven. The risk of extrapyramidal side effects with risperidone is moderate or low at doses below 6 mg/day. Its short half-life usually requires potentially inconvenient divided daily dosing. Amperozide and several additional mixed D2/5-HT_2 antagonists are in development (Gerlach, 1991; Meltzer, 1992).

Other approaches to innovation in developing antipsychotic agents include novel modifications of cerebral dopamine function, such as the use of partial agonists with preferential effects at presynaptic D2 autoreceptors (Baldessarini, 1996b; Meltzer, 1992). Examples include preclamol (S[−]-3-PPP), the aminoergoline SDZ-MAR-327, pramipexole (SND-919), and S(+)-11-hydroxy-N-n-propylnoraporphine. Some compounds thought to be selective D2 antagonists have surprisingly limited risk of extrapyramidal side effects, perhaps in part due to effects at serotonin receptors. Examples include emonapride, eticlopride, raclopride, and remoxipride; licensing of remoxipride was postponed because of a rare association with aplastic anemia. Substituted, enantiomeric R(+)-benzazepines show high selectivity for D1 dopamine receptors; these include the experimental compounds SKF-83566 and SCH-23390, and the latter's longer-acting tetracyclic analog SCH-39166. These agents are useful as experimental ligands, but their clinical actions remain uncertain (Daly and Waddington, 1992; Neumeyer *et al.*, 1992).

Finally, discovery of several gene products that appear to represent new dopamine receptor subtypes encourages a search for agents selective for them. Notably, D3 receptors are distributed preferentially in limbic forebrain (Baldessarini, 1996b; Civelli *et al.*, 1993; Gingrich and Caron, 1993). Partially D3-selective agents include several hydroxyaminotetralins (particularly, R[+]-7-hydroxy-N,N-dipropylaminotetralin, its congeners, and a tricyclic analog PD-128,907) and hexahydrobenzophenanthridines, with others in development (Baldessarini, 1996b; Baldessarini *et al.*, 1993; Waters *et al.*, 1993; Watts *et al.*, 1993). D4 dopamine receptors also are of interest because of their very low prevalence in the extrapyramidal basal ganglia and their selectivity for clozapine and S(+)-aporphines, which appear to be selective limbic dopamine antagonists (Baldessarini, 1996b; Van Tol *et al.*, 1991).

Innovative prospects for the treatment of anxiety disorders include extensions of the pharmacology of benzodiazepines (Potokar and Nutt, 1994). Recent advances in a molecular understanding of the $GABA_A$ receptor–benzodiazepine receptor–Cl^- channel complex indicate that this ring-shaped collection of transmembrane proteins includes representatives of at least 16 subunit proteins in five groups (α, β, γ, δ, ρ); benzodiazepines are believed to bind to α subunits and GABA to β subunits. Various combinations of the subunits occur in different cell populations (*e.g.*, those containing the combination of α_1, β_2, γ_2 represent benzodiazepine receptor type I, or ω_1, characteristic of cerebellum; types ω_2, less prevalent in CNS, and ω_3 occur in peripheral tissues including liver). This complexity may provide leads to receptor subtype- or even regionally selective agents with improved pharmacological properties (*see also* Chapter 17). Ligands for specific benzodiazepine receptor types include some nonbenzodiazepines. One, alpidem, an imidazole pyridine, is ω_1- and ω_3-selective and has useful anxiolytic activity in human beings, but hepatic toxicity prompted its discontinuation. Alternatively, some benzodiazepine derivatives have been found to have central anticholecystokinin activity; cholecystokinin has been implicated as a biological substrate for anxiety, and antagonists have been proposed as potential antianxiety agents (Browne and Shaw, 1991).

A particularly encouraging approach is the development and clinical testing of benzodiazepine receptor ligands with agonist activity intermediate between a full ag-

onist such as diazepam and an antagonist such as flumazenil (*see* Chapter 17; Browne and Shaw, 1991; Potokar and Nutt, 1994). Benzodiazepines and β-carbolines can have various agonist, partial-agonist, inverse agonist (reduce GABA effects on Cl^- influx), and antagonist (block full, partial, and inverse agonists) actions. Some with partial-agonist activity appear to have useful antianxiety effects with low risks of excessive sedation and cognitive impairment, or tolerance and dependence. Alpidem is an ω_1 partial agonist; other examples of benzodiazepine partial agonists include the imidazole benzodiazepines bretazenil and imidazenil. Bretazenil reportedly shows antipanic activity even when taken intermittently, with low abuse potential or risk of dependence. Other partial agonists that are not benzodiazepine derivatives include the β-carboline abecarnil and heterocyclic pazinaclone. Abecarnil also is selective for particular benzodiazepine receptor subtypes.

The recent development of several innovative psychotropic agents believed to act through central serotonergic neurotransmission (*e.g.*, buspirone, risperidone, uptake-inhibiting antidepressants) and elucidation of a growing range of serotonin receptor subtypes and agents that interact with them have strongly encouraged development of additional psychotropic agents acting on the serotonin system. One approach includes further development of azapirone analogs as 5-HT_{1A} ligands. Another is the use of 5-HT_3 antagonists; some modulate dopamine synthesis and release, and others have shown properties in animal tests that suggest antianxiety activity. Agents with anti-5-HT_3-selective activity include the short-term antiemetic compound ondansetron and the benzamide zacopride; many others are known but have been subjected to only limited clinical testing in psychiatric disorders including psychosis and anxiety.

Other approaches to the pharmacotherapy of anxiety disorders have included the use of antiadrenergic compounds usually employed for hypertension or other cardiovascular indications, including the β-adrenergic antagonists propranolol and atenolol and the α_2 agonist clonidine (*see* Chapter 10). Such compounds have not proven to be highly effective in severe anxiety disorders, but may modify autonomic expression of situational phobias such as performance anxiety (Dubovsky, 1990; Rickels and Schweizer, 1987). A technical aspect of the study of antianxiety agents has been the introduction of various laboratory procedures that can induce panic-like symptoms in a controlled setting as a basis for testing new anti-panic treatments (Gorman *et al.*, 1987).

It is reasonable to anticipate that the rapid expansion of novel macromolecular target sites for CNS drug innovation may lead to innovative principles and agents for treating psychoses and anxiety disorders in the future (Baldessarini, 1996a; Williams, 1991).

For further discussion of mental disorders, *see* Chapter 389 in *Harrison's Principles of Internal Medicine*, 13th ed., McGraw-Hill, New York, 1994.

Addonizio, G., Susman, V.L., and Roth, S.D. Neuroleptic malignant syndrome: review and analysis of 115 cases. Biol. Psychiatry, **1987**, *22*:1004–1020.

Alvir, J.M.J., Jeffrey, P.H., Lieberman, J.A., Safferman, A.Z., Schwimmer, J.L., and Schaaf, J.A. Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *N. Engl. J. Med.*, **1993**, *329*:162–167.

Arana, G.W., Goff, D.C., and Baldessarini, R.J. Efficacy of anticholinergic prophylaxis of neuroleptic-induced acute dystonia. *Am. J. Psychiatry*, **1988**, *145*:993–996.

Aubree, J.C., and Lader, M.H. High and very high dosage antipsychotics: a critical review. *J. Clin. Psychiatry*, **1980**, *41*:341–350.

Baldessarini, R.J. Enhancing treatment with psychotropic medicines. *Bull. Menninger Clinic*, **1994**, *58*:224–241.

Baldessarini, R.J., Cohen, B.M., and Teicher, M.H. Significance of neuroleptic dose and plasma level in the pharmacologic treatment of psychoses. *Arch. Gen. Psychiatry*, **1988**, *45*:79–91.

Baldessarini, R.J., and Frankenburg, F.R. Clozapine—a novel antipsychotic agent. *New Engl. J. Med.*, **1991**, *324*:746–754.

Baldessarini, R.J., Kula, N.S., McGrath, C.R., Bakthavachalam, V., Kebabian, J.W., and Neumeyer, J.L. Isomeric selectivity at dopamine D_3 receptors. *Eur. J. Pharmacol.*, **1993**, *239*:269–270.

Ben-Jonathan, N. Dopamine, a prolactin inhibiting hormone. *Endocrine Rev.*, **1985**, *6*:564–589.

Berger, F.M. The pharmacological properties of 2-methyl-2-n-propyl-1,3 propanediol dicarbamate (MILTOWN), a new interneuronal blocking agent. *J. Pharmacol. Exp. Ther.*, **1954**, *112*:413–423.

Biederman, J., Baldessarini, R.J., Wright, V., Knee, D., and Harmatz, J. A double-blind placebo-controlled study of desipramine in the treatment of attention deficit disorder: I. Efficacy. *J. Am. Acad. Child Adolesc. Psychiatry*, **1989**, *28*:777–784.

Biederman, J., and Jellinek, M.S. Psychopharmacology in children. *N. Engl. J. Med.*, **1984**, *310*:968–972.

Brogden, R.N., and Goa, K.L.: Flumazenil: preliminary review of its benzodiazepine antagonist properties, intrinsic activity, and therapeutic use. *Drugs*, **1988**, *35*:448–467.

Brotman, A.W., Falk, W.E., and Gelenberg, A.J. Pharmacologic treatment of acute depressive subtypes. In, *Psychopharmacology: The Third Generation of Progress*. (Meltzer, H.Y., ed.) Raven Press, New York, **1987**, pp. 1031–1040.

Bunney, B.S., Sesack, S.R., and Silva, N.L. Midbrain dopaminergic systems: neurophysiology and electrophysiological pharmacology. In, *Psychopharmacology: The Third Generation of Progress.* (Meltzer, H.Y., ed.) Raven Press, New York, **1987,** pp. 113–126.

Burt, D.R., and Kamatchi, G.L. GABAA receptor subtypes: from pharmacology to molecular biology. *FASEB J.,* **1991,** *5*:2916–2923.

Cade, J.F.J. Lithium salts in the treatment of psychotic excitement. *Med. J. Aust.,* **1949,** *2*:349–352.

Carlsson, A. Early psychopharmacology and the rise of modern brain research. *J. Psychopharmacology,* **1990,** *4*:120–126.

Chan, C.H., Janicak, P.G., Davis, J.M., Altman, E., Andriukaitis, S., and Hedeker, D. Response of psychotic and nonpsychotic depressed patients to tricyclic antidepressants. *J. Clin. Psychiatry,* **1987,** *48*:197–200.

Chouinard, G., Jones, B., Remington, G., Bloom, D., Addington, D., MacEwan, G.W., Labelle, A., Beauclair, L., and Arnott, W. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J. Clin. Psychopharmacology,* **1993,** *13*:25–40.

Cohen, B.M., and Lipinski, J.F. *In vivo* potencies of antipsychotic drugs in blocking alpha-1 noradrenergic and dopamine D-2 receptors: implications for drug mechanisms of action. *Life Sci.,* **1986,** *39*: 2571–2580.

Cohen, B.M., Tsuneizumi, T., Baldessarini, R.J., Campbell, A., and Babb, S.M. Differences between antipsychotic drugs in persistence of brain levels and behavioral effects. *Psychopharmacology,* **1992,** *108*: 338–344.

Coplan, J.D., Gorman, J.M., and Klein, D.F. Serotonin related functions in panic-anxiety: a critical overview. *Neuropsychopharmacology,* **1992,** *6*:189–200.

Creese, I., Burt, D.R., and Snyder, S.H. Biochemical actions of neuroleptic drugs: focus on dopamine receptor. In, *Handbook of Psychopharmacology,* vol. 10. (Iversen, L.L., Iversen, S.D., and Snyder, S.H., eds.) Plenum Press, New York, **1978,** pp. 37–89.

Czeizel, A., and Lendvay, A. Lack of teratogenic effects of benzodiazepines. *Lancet,* **1987,** *1*:628.

Dabiri, L.M., Pasta, D., Darby, J.K., and Mosbacher, D. Effectiveness of vitamin E for treatment of long-term tardive dyskinesia. *Am. J. Psychiatry,* **1994,** *151*:925–926.

Daly, S.A., and Waddington, J.L. Two directions of dopamine D1/D2 receptor interaction in studies of behavioural regulation: a finding generic to four new, selective dopamine D1 receptor antagonists. *Eur. J. Pharmacol.,* **1992,** *213*:251–258.

Delay, J., and Deniker, P. Trente-huit cas de psychoses traitées par la cure prolongée et continue de 4560 RP. Le Congrès des Al. et Neurol. de Langue Fr. In, *Compte rendu du Congrès.* Masson et Cie, Paris, **1952.**

Dubovsky, S.L. Generalized anxiety disorder: new concepts and psychopharmacologic therapies. *J. Clin. Psychiatry,* **1990,** *51 Suppl.*: 3–10.

Erle, G., Basso, M., Federspil, G., Sicolo, N., and Scandellari, C. Effect of chlorpromazine on blood glucose and plasma insulin in man. *Eur. J. Clin. Pharmacol.,* **1977,** *11*:15–18.

Forsman, A., and Öhman, R. On the pharmacokinetics of haloperidol. *Nord. Psykiatr. Tidskr.,* **1974,** *28*:441–448.

Gardos, G., Casey, D.E., Cole, J.O., Perenyi, A., Kocsis, E., Arato, M., Samson, J.A., and Conley C. Ten-year outcome in tardive dyskinesia. *Am. J. Psychiatry,* **1994,** *151*:836–841.

Gerlach, J. New antipsychotics: classification, efficacy and adverse effects. *Schizophrenia Bull.,* **1991,** *17*:289–309.

Goff, D.C., and Baldessarini, R.J. Drug interactions with antipsychotic agents. *J. Clin. Psychopharmacol.* **1993,** *13*:57–67.

Gorman, J.M., Fyer, M.R., Liebowitz, M.R., and Klein, D.F. Pharmacologic provocation of panic attacks. In, *Psychopharmacology: The Third Generation of Progress.* (Meltzer, H.Y., ed.) Raven Press, New York, **1987,** pp. 985–993.

Greenblatt, D.J., and Shader, R.I. Meprobamate: A study of irrational drug use. *Am. J. Psychiatry,* **1971,** *127*:1297–1303.

Greenblatt, D.J., Shader, R.I., and Abernethy, D.R. Drug therapy: current status of benzodiazepines. *N. Engl. J. Med.,* **1983,** *309*:354–358, 410–416.

Greenblatt, D.J., Shader, R.I., Divoll, M., and Harmatz, J.S. Benzodiazepines: a summary of pharmacokinetic properties. *Br. J. Clin. Pharmacol.,* **1981,** *11* Suppl.:11S–16S.

Herz, M.I., Glazer, W.M., Mostert, M.A., Sheard, M.A., Szymanski, H.V., Hafez, H., Mirza, M., and Vana, J. Intermittent vs. maintenance medication in schizophrenia. *Arch. Gen. Psychiatry,* **1991,** *48*:333–339.

Hoehn-Saric, R. Neurotransmitters in anxiety. *Arch. Gen. Psychiatry,* **1982,** *39*:735–742.

Janssen, P.A.J. The evolution of the butyrophenones, haloperidol and trifluperidol, from meperidine-like 4-phenylpiperidines. *Int. Rev. Neurobiol.,* **1965,** *8*:221–263.

Jus, K., Jus, A., Gautier, J., Villeneuve, A., Pires, P., Pineau, R., and Villeneuve, R. Studies of the actions of certain pharmacological agents on tardive dyskinesia and on the rabbit syndrome. *Int. J. Clin. Pharmacol. Ther. Toxicol.,* **1974,** *9*:138–145.

Kane, J.M., Rifkin, A., Woerner, M., Reardon, G., Sarantakos, S., Schiebel, D., and Ramos-Lorenzi, J. Low-dose neuroleptic treatment of outpatient schizophrenics. *Arch. Gen. Psychiatry,* **1983,** *40*:893–896.

Kline, N.S. Clinical experience with iproniazid (MARSILID). *J. Clin. Exp. Psychopathol.,* **1958,** *19 Suppl.*:72–78.

Knapp, M.J., Knopman, D.S., Solomon, P.R., Pendlebury, W.W., Davis, C.S., and Gracon, S.I. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. *JAMA,* **1994,** *271*:985–991.

Korpi, E.R., Phelps, B.H., Granger, H., Chang, W.-H., Linnoila, M., Meek, J.L., and Wyatt, R.J. Simultaneous determination of haloperidol and its reduced metabolite in serum and plasma by isocratic liquid chromatography with electrochemical detection. *Clin. Chem.,* **1983,** *29*:624–628.

Kuhn, R. The treatment of depressive states with G22355 (imipramine hydrochloride). *Am. J. Psychiatry,* **1958,** *115*:459–464.

Laborit, H., Huguenard, P., and Alluaume, R. Un nouveau stabilisateur végétatif (LE 4560 RP). *Presse Méd.,* **1952,** *60*:206–208.

Lader, M. Benzodiazepines: a risk-benefit profile. *CNS Drugs,* **1994,** *1*:377–387.

Lader, M., and Olajide, D. A comparison of buspirone and placebo in relieving benzodiazepine withdrawal symptoms. *J. Clin. Psychopharmacol.,* **1987,** *7*:11–15.

Laegreid, L., Hagberg, G., and Lundberg, A. The effect of benzodiazepines on the fetus and the newborn. *Neuropediatrics,* **1992,** *23*:18–23.

Leysen, J.E., Janssen, P.M.F., Megens, A.A.H.P., and Schotte, A. Risperidone: a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. *J. Clin. Psychiatry,* **1994,** *55 Suppl.* 5:5–12.

Lipinski, J.F., Jr., Zubenko, G.S., Cohen, B.M., and Barreira, P.J. Propranolol in the treatment of neuroleptic-induced akathisia. *Am. J. Psychiatry,* **1984,** *141*:412–415.

Meltzer, H.Y., and Lowy, M.T. The serotonin hypothesis of depression. In, *Psychopharmacology: The Third Generation of Progress.* (Meltzer, H.Y., ed.) Raven Press, New York, **1987,** pp. 513–526.

Moore, K.E. Hypothalamic dopaminergic neuronal systems. In, *Psy-*

chopharmacology: The Third Generation of Progress. (Meltzer, H.Y., ed.) Raven Press, New York, **1987**, pp 127–139.

Moore, N.A., Tye, N.C., Axton, M.S., and Risius, F.C. The behavioral pharmacology of olanzapine, a novel "atypical" antipsychotic agent. *J. Pharmacol. Exp. Ther.*, **1992**, *262*: 545–551.

Morgenstern, H., and Glazer, W.M. Identifying risk factors for tardive dyskinesia among long-term outpatients maintained with neuroleptic medications. *Arch. Gen. Psychiatry*, **1993**, *50*: 723–733.

Neumeyer, J.L., Kula, N.S., Baldessarini, R.J., and Baindur, N. Stereoisomeric probes for the D1 dopamine receptor: synthesis and characterization of *R*-(+) and *S*-(−) enantiomers of 3-allyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine and its 6-bromo analogue. *J. Med. Chem.*, **1992**, *35*:1466–1471.

Overall, J.E. Prior psychiatric treatment and the development of breast cancer. *Arch. Gen. Psychiatry*, **1978**, *35*:898–899.

Pearlman, C.A. Neuroleptic malignant syndrome: a review of the literature. *J. Clin. Psychopharmacology*, **1986**, *6*:257–273.

Potokar, J., and Nutt, D.J. Anxiolytic potential of benzodiazepines receptor partial agonists. *CNS Drugs*, **1994**, *1*:305–315.

Ray, W.A., Griffin, M.R., Schaffner, W., Baugh, D.K., and Milton, L.J., III. Psychotropic drug use and the risk of hip fracture. *N. Engl. J. Med.*, **1987**, *316*:363–369.

Rickels, K., and Schweizer, E.E. Current pharmacotherapy of anxiety and panic. In, *Psychopharmacology: The Third Generation of Progress.* (Meltzer, H.Y., ed.) Raven Press, New York, **1987**, pp. 1193–1203.

Rickels, K., Schweizer, E., Csanalosi, I., Case, W.G., and Chung, H. Long-term treatment of anxiety and risk of withdrawal: prospective comparison of chlorazepate and buspirone. *Arch. Gen. Psychiatry*, **1988**, *45*:444–450.

Rosenbaum, J.F. (ed.) New uses for clonazepam in psychiatry: introduction and overview. *J. Clin. Psychiatry*, **1987**, *48 Suppl. 3*:1–56.

Rotrosen, J., Angrist, B. M., Gershon, S., Aronson, M., Gruen, P., Sachar, E.J., Denning, R.K., Matthysse, S., Stanley, M., and Wilk, S. Thiethylperazine: clinical antipsychotic efficacy and correlation with potency in predictive systems. *Arch. Gen. Psychiatry*, **1978**, *35*:1112–1118.

Rubin, R.T. Prolactin in schizophrenia. In, *Psychopharmacology: The Third Generation of Progress.* (Meltzer, H.Y., ed.) Raven Press, New York, **1987**, pp. 803–808.

Sachar, E.J. Neuroendocrine responses to psychotropic drugs. In, *Psychopharmacology: A Generation of Progress.* (Lipton, M.A., DiMascio, A., and Killam, K.F., eds.) Raven Press, New York, **1978**, pp. 499–507.

Sampath, G., Shah, A., Krska, J., and Soni, S.D. Neuroleptic discontinuation in the very stable schizophrenic patient: relapse rates and serum neuroleptic levels. *Hum. Psychopharmacol. Clin. Exp.*, **1992**, *7*: 255–264.

Sedvall, G. The current status of PET scanning with respect to schizophrenia. *Neuropsychopharmacology*, **1992**, *7*:41–54.

Seeman, P. Brain dopamine receptors. *Pharmacol. Rev.*, **1980**, *32*:229–313.

Shapiro, R.M. Regional neuropathology in schizophrenia: where are we? Where are we going? *Schizophrenia Res.*, **1993**, *10*:187–239.

Simpson, G.M., Cooper, T.B., Bark, N., Sud, I., and Lee, J.H. Effect of antiparkinsonian medication on plasma levels of chlorpromazine. *Arch. Gen. Psychiatry*, **1980**, *37*:205–208.

Snyder, S.H., and Yamamura, H.I. Antidepressants and the muscarinic acetylcholine receptor. *Arch. Gen. Psychiatry*, **1977**, *34*:236–239.

Sokoloff, P., Giros, B., Martres, M.P., Bouthenet, M.L., and Schwartz, J.C. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. *Nature*, **1990**, *347*:146–151.

Spencer, T., Biederman, J., Wilens, T., Steingard, R., and Geist, D. Nortriptyline treatment of children with attention-deficit hyperactivity disorder and tic disorder or Tourette's syndrome. *J. Am. Acad. Child Adolesc. Psychiatry*, **1993**, *32*:205–210.

Sulser, F., and Robinson, S.E. Clinical implications of pharmacological differences among antipsychotic drugs (with particular emphasis on biochemical central synaptic adrenergic mechanisms). In, *Psychopharmacology: A Generation of Progress.* (Lipton, M.A., DiMascio, A., and Killam, K.F., eds.) Raven Press, New York, **1978**, pp. 943–954.

Sussman, N. The uses of buspirone in psychiatry. Symposium. Buspirone: seven year update (1993, Philadelphia, Pennsylvania). *J. Clin. Psychiatry Monogr.*, **1994**, *12*:3–21.

Taylor, D.P. Buspirone, a new approach to the treatment of anxiety. *FASEB J.*, **1988**, *2*:2445–2452.

Tsuneizumi, T., Babb, S.M., and Cohen, B.M. Drug distribution between blood and brain as a determinant of antipsychotic drug effects. *Biol. Psychiatry*, **1992**, *32*:817–824.

Tyrer, P.J. Use of β-blocking drugs in psychiatry and neurology. *Drugs*, **1980**, *20*:300–308.

Van Tol, H.H., Bunzow, J.R., Guan, H.C., Sunahara, R.K., Seeman, P.K., Niznik, H.B., and Civelli, O. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature*, **1991**, *350*:610–614.

Waters, N., Lagerkvist, S., Löfberg, L., Piercey, M., and Carlsson, A. The dopamine D3 receptor and autoreceptor preferring antagonists (+)-AJ76 and (+)-UH232: a microdialysis study. *Eur. J. Pharmacol.*, **1993**, *242*:151–163.

Watts, V.J., Lawler, C.P., Knoerzer, T., Mayleben, M.A., Neve, K.A., Nichols, D.E., and Mailman R.B. Hexahydrobenzo[a]phenanthridines: novel dopamine D3 receptor ligands. *Eur. J. Pharmacol.*, **1993**, *239*:271–273.

Williams, M. Challenges in the search for CNS therapeutics in the 1990s. *Curr. Opinion Ther. Patents*, **1991**, *1*:693–723.

Wolkin, A., Brodie, J.D., Barouche, F., Rotrosen, J., Wolf, A.P., Smith, M., Fowler, J., and Cooper, T.B. Dopamine receptor occupancy and plasma haloperidol levels. *Arch. Gen. Psychiatry*, **1989**, *46*:482–484.

Yocca, F.D. Neurochemistry and neurophysiology of buspirone and gepirone: interactions at presynaptic and postsynaptic 5-HT_{1A} receptors. *J. Clin. Psychopharmacology*, **1990**, *10 Suppl. 3*:6S–12S.

Zarate, C.A., Tohen, M., and Baldessarini, R.J. Clozapine therapy in severe mood disorders. *J. Clin. Psychiatry*, **1995** (in press).

MONOGRAPHS AND REVIEWS

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV.* 4th ed., Revised. APA Press, Inc., Washington, D.C., **1994**.

Ayd, F.J., Jr., and Blackwell, B. (eds.). *Discoveries in Biological Psychiatry.* J. B. Lippincott Co., Philadelphia, **1970**.

Baldessarini, R.J. Antipsychotic agents. In, *The Psychiatric Therapies.* (Karasu, T.B., ed.) American Psychiatric Association, Washington, D.C., **1984b**, pp. 119–170.

Baldessarini, R.J. Fifty years of biomedical psychiatry and psychopharmacology in America. In, *Fifty Years of American Psychiatry.* (Menninger R., and Nemiah, J., eds.) American Psychiatric Press, Washington, D.C., **1996a**.

Baldessarini, R.J. *Chemotherapy in Psychiatry: Principles and Practice*, 2nd ed. Harvard University Press, Cambridge, MA, **1996b**.

Baldessarini, R.J., Cohen, B.M., and Teicher, M.H. Pharmacological treatment. In, *Schizophrenia: Treatment of Acute Psychotic Episodes.* (Levy,

S.T., and Ninan, P.T., eds.) American Psychiatric Press, Washington, D.C., **1990**, pp. 61–118.

Baldessarini, R.J., Cole, J.O., Davis, J.M., Gardos, G., Simpson, G., and Tarsy, D. *Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association. Task Force Report.* No. 18. American Psychiatric Association, Washington, D.C., **1980**.

Baldessarini, R.J., and Tarsy, D. Relationship of the actions of neuroleptic drugs to the pathophysiology of tardive dyskinesia. *Int. Rev. Neurobiol.*, **1979**, *21*:1–45.

Bitton, R., and Schneider, B. Endocrine, metabolic, and nutritional effects of psychotropic drugs. In, *Adverse Effects of Psychotropic Drugs.* (Kane, J.M., and Lieberman, J.A., eds.) Guilford Press, New York, **1992**, pp. 341–355.

Browne, L.J., and Shaw, K.J. New anxiolytics. *Ann. Rep. Med. Chem.* **1991**, *26*:1–10.

Caldwell, A.E. History of psychopharmacology. In, *Principles of Psychopharmacology,* 2nd ed. (Clark, W.G., and del Giudice, J., eds.) Academic Press, Inc., New York, **1978**, pp. 9–40.

Chase, T.N. Rational approaches to the pharmacotherapy of chorea. In, *The Basal Ganglia.* (Yahr, M.D., ed.) *Association for Research in Nervous and Mental Disease Research Publications,* Vol. 55. Raven Press, New York, **1976**, pp. 337–350.

Civelli, O., Bunzow, J.R., and Grandy, D.K. Molecular diversity of the dopamine receptors. *Ann. Rev. Pharmacol. Toxicol.*, **1993**, *31*: 281–307.

Cooper, T.B., Simpson, G.M., and Lee, J.H. Thymoleptic and neuroleptic drug plasma levels in psychiatry: current status. *Int. Rev. Neurobiol.*, **1976**, *19*:269–309.

Efron, D.H., Holmstedt, B., and Kline, N.S. (eds.). *Ethnopharmacologic Search for Psychoactive Drugs.* Public Health Service Publication No. 67-1645. U.S. Government Printing Office, Washington, D.C., **1967**.

Eison, M.S. Use of animal models: toward anxioselective drugs. *Psychopathology,* **1984**, *17 Suppl. 1*:37–44.

Fielding, S., and Lal, H. Behavioral actions of neuroleptics. In, *Handbook of Psychopharmacology,* vol. 10. (Iversen, L.L., Iversen, S.D., and Snyder, S.H., eds.) Plenum Press, New York, **1978**, pp. 91–128.

Gingrich, J.A., and Caron, M.G. Recent advances in the molecular biology of dopamine receptors. *Ann. Rev. Neuroscience,* **1993**, *16*:299–321.

Goldberg, H.L. Benzodiazepine and nonbenzodiazepine anxiolytics. *Psychopathology,* **1984**, *17 Suppl. 1*:45–55.

Hollister, L.E., Müller-Oerlinghausen, B., Rickels, K., and Shader, R.I. (eds.) Clinical uses of benzodiazepines. *J. Clin. Psychopharmacology,* **1993**, *13 Suppl. 1*:1–169.

Itil, T.M. Effects of psychotropic drugs on qualitatively and quantitatively analyzed human EEG. In, *Principles of Psychopharmacology,* 2nd ed. (Clark, W.G., and del Giudice, J., eds.) Academic Press, Inc., New York, **1978**, pp. 261–277.

Janicak, P.G., Davis, J.M., Preskorn, S.H., and Ayd, F.J., Jr. *Principles and Practice of Psychopharmacotherapy.* The Williams & Wilkins Co., Baltimore, **1993**.

Janssen, P.A.J. Butyrophenones and diphenylbutylpiperidines. In, *Psychopharmacological Agents,* Vol. 3. (Gordon, M., ed.) Academic Press, Inc., New York, **1974**, pp. 128–158.

Janssen, P.A.J., and Van Bever, W.F. Preclinical psychopharmacology of neuroleptics. In, *Principles of Psychopharmacology,* 2nd ed. (Clark, W.G., and del Giudice, J., eds.) Academic Press, Inc., New York, **1978**, pp. 279–295.

Jenike, M.A. *Handbook of Geriatric Psychopharmacology.* PSG Publishing Co., Littleton, MA, **1985**.

Kane, J.M., Jeste, D.V., Barnes, T.R.E., Casey, D.E., Cole, J.O., Davis, J.M., Gualtieri, C.T., Schooler, N.R., Sprague, R.L., and Wettste- R.M. *Tardive Dyskinesia. A Task Force Report of the American Psychiatric Association.* American Psychiatric Association, Washington, D.C., **1992**.

Kaplan, H.I., and Sadock, B.J. (eds.). *Comprehensive Textbook of Psychiatry,* 5th ed. The Williams & Wilkins Co., Baltimore, **1989**.

Lewin, L. *Phantastica, Narcotic and Stimulating Drugs: Their Use and Abuse.* Berlin, **1924**, English translation, London, **1931**, E. P. Dutton & Co., New York, **1931**.

Meltzer, H.Y. (ed.) *Novel Antipsychotic Drugs.* Raven Press, New York, **1992**.

Morselli, P.L. Psychotropic drugs. In, *Drug Disposition During Development.* (Morselli, P.L., ed.) Spectrum Publications, Inc., New York, **1977**, pp. 431–474.

Neumeyer, J.L., and Booth, R.G. Neuroleptics and anxiolytic agents. In, *Principles of Medicinal Chemistry,* 4th ed. (Foye, W.O., Williams, D.A., and Lemke, T.L., eds.) Williams & Wilkins, Baltimore, 1995 (in press).

Polc, P. Electrophysiology of benzodiazepine receptor ligands: multiple mechanisms and sites of action. *Prog. Neurobiol.*, **1988**, *31*:349–42-

Popper, C. (ed.). *Psychiatric Pharmacosciences of Children and Adolescents.* American Psychiatric Press, Washington, D.C., **1987**.

Prien, R.F. Chemotherapy in chronic organic brain syndrome—a review of the literature. *Psychopharmacol. Bull.*, **1973**, *9*:5–20.

Raskin, A., Robinson, D.S., and Levine, J. *Age and the Pharmacology of Psychoactive Drugs.* Elsevier-North Holland, Inc., New York, 1981.

Rivera-Calimlim, L., and Hershey, L. Neuroleptic concentrations and clinical response. *Annu. Rev. Pharmacol. Toxicol.*, **1984**, *24*:361–386.

Shapiro, A.K., Shapiro, E.S., Young, J.G., and Feinberg, T.E. *Gilles de la Tourette Syndrome.* Raven Press, New York, **1988**.

Shore, P.A., and Giachetti, A. Reserpine: basic and clinical pharmacology. In, *Handbook of Psychopharmacology,* Vol. 10. (Iversen, L.L., Iversen, S.D., and Snyder, S.H., eds.) Plenum Press, New York, 1978, pp. 197–219.

Swazey, J.P. *Chlorpromazine in Psychiatry: A Study in Therapeutic Innovation.* M.I.T. Press, Cambridge, MA, **1974**.

Symposium. (Various authors.) *Pharmacology of Benzodiazepines.* (Usdin, E., Skolnick, P., Tallman, J.F., Jr., Greenblatt, D., and Paul, S.M., eds.) Macmillan Press Ltd., London, **1982**.

Symposium. (Various authors.) *Anxiolytes: Neurochemical, Behavioral and Clinical Perspectives.* (Enna, S.J., Malick, J.B., and Yamamura, H.I., eds.) Raven Press, New York, **1983**.

Symposium. (Various authors.) Chloride channels and their modulation by neurotransmitters and drugs. (Biggio, G., and Costa, E., eds.) *Adv. Biochem. Psychopharmacol.*, **1988**, *45*:1–384.

Tarsy, D., and Baldessarini, R.J. Movement disorders induced by psychotherapeutic agents. Clinical features, pathophysiology, and management. In, *Movement Disorders.* (Shah, N.S., and Donald, A.G., eds.) Plenum Press, New York, **1986**, pp. 365–389.

Weil-Malherbe, H. The biochemistry of the functional psychoses. *Adv. Enzymol. Relat. Areas Mol. Biol.*, **1967**, *29*:479–553.

Wolf, M.E., and Roth, R.H. Dopamine autoreceptors. In, *Dopamine Receptors:* (Creese, I., and Fraser, C.M., eds.). *Receptor Biochemistry and Methodology,* Vol. 8. Alan R. Liss, Inc., New York, **1987**, pp. 45–96.

Woods, J.H., Katz, J.L., and Winger, G. Abuse liability of benzodiazepines. *Pharmacol. Rev.*, **1987**, *39*:251–413.

Zametkin, A.J., and Rapoport, J.L. Noradrenergic hypothesis of attention deficit disorder with hyperactivity: a critical review. In, *Psychopharmacology: The Third Generation of Progress.* (Meltzer, H.Y., ed.) Raven Press, New York, **1987**, pp. 837–842.